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Original Communications

A STATISTICAL COMPARISON OF NORMAL BALLISTOCARDIOGRAMS RECORDED WITH A HIGH-FREQUENCY TABLE AND WITH VARIOUS INSTRUMENTS WHICH RECORD BODY MOTION DIRECTLY

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BALLISTOCARDIOGRAMS obtained with any one of several devices originally developed by Dock and Taubman[1] which record the motion of a bar placed across the shins qualitatively resemble tracings obtained with a high-frequency table of the type introduced by Starr.[2] In order to estimate the degree of resemblance quantitatively, we obtained measurements of certain wave segments of tracings of normal subjects recorded simultaneously with a high-frequency table and with each of three different types of Dock instruments. From this study we hoped to obtain specific information bearing on certain theoretical and practical aspects of recording body motion with these devices.

MATERIALS AND METHODS

The high-frequency critically damped table used in this study has been completely described.[3] It utilizes a Statham strain gauge, the output of which is amplified by a Brush amplifier. The displacement tracing is recorded on one channel of a Brush recorder. The outputs of the three instruments utilizing direct body recording were amplified by a Sanborn Viso-Cardiette and recorded

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on the second channel of the Brush recorder. These instruments consisted of: (1) a photoelectric ballistocardiograph[4] manufactured by the Sanborn Company. When this instrument is in use, the light source, mounted on the crosspiece, moves with reference to a stationary photoelectric cell. It produces a displacement tracing. The built-in filter was used in all tracings to minimize undulations of the base line with respiration. (2) A piezoelectric ballistocardiograph[5] manufactured by the John Peck Laboratories. It measures body movements in terms of displacement. (3) An electromagnetic ballistocardiograph manufactured by J. Everett Hill. If unfiltered, such an instrument produces a velocity tracing. However, the instrument used in this study contains a filter in the form of a 20 microfarad capacitor which almost completely integrates the velocity trace into one of displacement type.[6] Comparison of simultaneous tracings obtained with this filtered instrument and with the bed showed homologous wave peaks to be in phase.

The table was standardized so that a 280 gram weight produced a displacement equivalent to a one centimeter deflection on the record. The amplifier (Viso-Cardiette) was adjusted so that the tracing obtained with one of the Dock type instruments showed an amplitude approximately equivalent to that of the tracing obtained with the table. This adjustment could not be made exactly, but the statistical studies were carried out in such a way as to eliminate variations in standardization as a source of error.

The statistical results to be reported are based on two groups of data:

A. Simultaneous tracings on ten normal individuals, four men and six women, aged 23 to 38.

B. Ten consecutive simultaneous tracings on one normal man.

In both A and B three sets of simultaneous tracings were obtained with the following: (1) table and photoelectric instrument; (2) table and piezoelectric instrument; (3) table and electromagnetic instrument. Figure 1 illustrates typical tracings obtained on a 27-year-old man.

In Part B, the direct-recording device was removed and replaced between each of the ten consecutive recordings, the sensitivity of the Viso-Cardiette remaining constant.

In Part A, the IJ and JK segments of 20 consecutive systoles were measured to the closest 0.5 mm. on each of the simultaneous records. The IJ and JK segments were chosen because they represent the prominent upstroke and prominent downstroke, respectively, of the normal ballistocardiogram. The ratio, JK:IJ, was also calculated for each of the complexes measured.

In Part B, the IJ and JK segments produced by twenty to twenty-five consecutive systoles were measured to the closest 0.5 mm. on each of the separate records. The measurements were started and stopped at the same point in the respiratory cycle as judged by the waxing and waning of the amplitude of the complexes. The same number of complexes was always measured in the two simultaneous tracings. The mean segment length for each individual record was determined. The mean IJ and JK segments were also expressed in the form of the mean JK:IJ ratio for each of the ten records. All measurements were made by the same individual.

Since all of the tracings obtained with the table were recorded simultaneously with the Dock type of instrument, it was obvious that the footboard of the table ordinarily utilized in routine ballistocardiography could not be used because it would damp the body motion picked up by direct recording. Therefore, all tracings obtained with the table were recorded without the footboard. This undoubtedly modifies the amplitude of waves recorded with the table. However, since this method of recording was constant for all tracings with the table, the basis for making comparative quantitative studies seemed sound. The maximum motion of the table is of the order of only 0.00015 inch.[3] Therefore, the ballistocardiographic table is, for practical purposes, as stable as any type of rigid table advocated for use with the direct-recording devices.

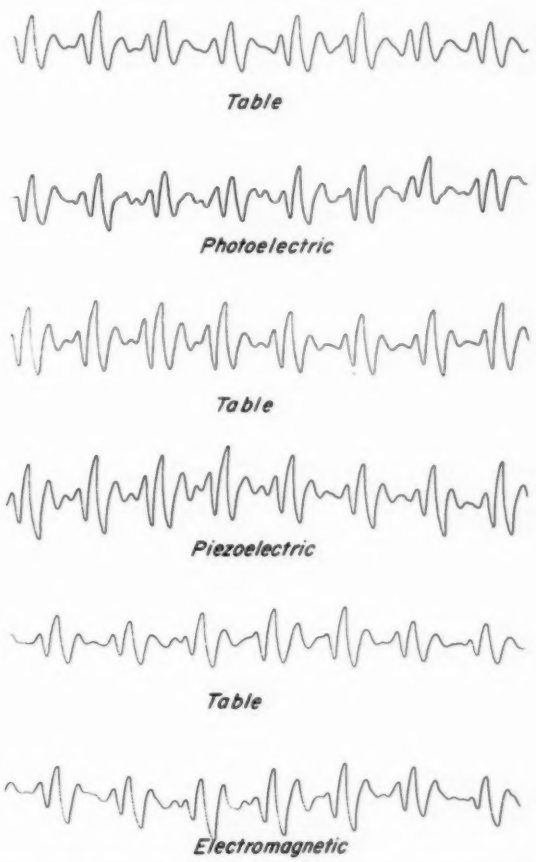

Fig. 1.—Normal man, aged 27. Typical comparative tracings obtained with a high-frequency ballistocardiographic table and with each of three types of instruments designed to record body motion directly. See text.

STATISTICAL RESULTS

Data From Part A.—

1. *Correlation between the two general methods of recording*: Correlation coefficients were calculated between the segments or ratio of each of the Dock

type instruments and the corresponding segment or ratio of the table and tested for significance by means of Fisher's z transformation.[7] There was a high degree of correlation between the table and each of the direct-recording devices for both the IJ and the JK segments. All probability values were below the 0.001 level except in the case of the IJ segment of a single subject with the photoelectric instrument; this value was, however, below the 0.01 level.

In the case of the JK:IJ ratio, the individual correlations between the table and each of the direct-recording devices were not striking. Probabilities for such correlations exceeded 0.05 for four individuals with the photoelectric instrument, three individuals with the piezoelectric instrument, and three individuals with the electromagnetic instrument.

The correlations obtained for individual subjects were not averaged because significant heterogeneity of the coefficients ($P < 0.02$) was demonstrated* in all instances except three. These three, for which P ranged between 0.10 and 0.20, consisted of the JK segment and the JK:IJ ratio recorded with the photoelectric instrument and IJ segment recorded with the electromagnetic device.

2. *Differences in the degree of correlation between each of the three direct recording devices and the table*: Tests of significance of the difference between correlations of each of the pickups and the table were carried out by means of the z transformation to determine whether one correlation was significantly superior to another.

In the case of the IJ segment the piezoelectric instrument yielded a significantly better correlation than the photoelectric instrument in two individuals ($P < 0.01$, < 0.02). In one subject the piezoelectric device showed a significantly better correlation than the electromagnetic instrument ($P < 0.01$) and a correlation with the latter significantly exceeded that of the photoelectric pickup in one subject ($P < 0.01$).

For the JK segment, the piezoelectric instrument demonstrated a significantly better correlation than the photoelectric in one instance ($P < 0.02$); the electromagnetic instrument correlated significantly better than the photoelectric in one subject ($P < 0.05$); the electromagnetic instrument showed a significantly higher correlation than the piezoelectric in one subject ($P < 0.05$).

In the case of the JK:IJ ratio, the correlations obtained with the piezoelectric instrument significantly exceeded those obtained with the photoelectric in two subjects ($P < 0.01$, < 0.02), and a correlation of the electromagnetic device significantly exceeded that of the photoelectric on one occasion ($P < 0.01$).

Thus, in no instance did the photoelectric instrument give a significantly better correlation with the table for IJ and JK segments or the JK:IJ ratio than did the other two devices.

3. *Degree of constancy in normal subjects of the JK:IJ ratio*: The variance of the JK:IJ ratio obtained for the ten subjects with each of the instruments

*The chi-square test used to determine the probability that the several correlations were not drawn from the same correlation parameter is that described by Snedecor;[7] it may be represented by the equation:

$$\text{Chi square} = S\left\{(n-3)\,z^2\right\} - \bar{z}S\left\{(n-3)\,z\right\}$$

where the degree of freedom is one less than the number of correlations tested.

utilizing direct body recording was compared with the variance of this ratio for corresponding tracings obtained with the table. In all cases the variance of this ratio from subject to subject was less with the direct pickup than with the bed. However, the variance ratio[7] showed that none of these differences approached significance.

4. *Variation in amplitude of IJ and JK segments with respiration*: The variance of the amplitude of the IJ segments of each individual recorded with each Dock type instrument was compared with the variance of the amplitude of this segment recorded simultaneously with the table by means of a variance ratio. A similar test was carried out for the JK segment. In no subject did such variance ratios approach statistical significance indicating that the variation in amplitude of these segments with respiration could not be demonstrated to be significantly greater or smaller with the direct-recording device than with the table.

Data From Part B.—

Reproducibility of consecutively recorded tracings with the instruments utilizing direct recording: These studies were designed to give information concerning inaccuracies arising from inability to place the direct-recording device uniformly in the same position for repeated tracings. The variance of the segments and of the ratio for a given instrument was compared with the variance of the corresponding segment or ratio simultaneously recorded with the table. In all instances the variability of repeated tracings with the three devices was greater than the variability of those with the table. However, the variance of the piezoelectric instrument did not significantly exceed the variance of the table for either of the segments or the ratio. The variance of the electromagnetic instrument was significantly greater than the variance of the table for the JK segment ($P < 0.02$) but not for the IJ segment or the ratio. The variance of the photoelectric instrument was significantly larger than the variance of the table for both the IJ ($P < 0.02$) and the JK ($P < 0.002$) segments but not for the JK:IJ ratio.

The variances of the mean segments and ratio with the various direct-recording instruments were also compared with each other. The variation of these measurements recorded with the table is assumed to depend solely upon the variation of the patient's heart action from record to record and thus to provide a control for the correction of that particular portion of the total variation obtained with each instrument. This correction was obtained by dividing the mean segment or ratio obtained with the direct-recording device by the corresponding mean segment or ratio obtained with the table for each of the 10 repeated records. The resultant 10 quotients were utilized for the determinations of the variances used in the variance ratios. There was no significant difference in the variances of the IJ segment or the JK:IJ ratio of the three direct-recording instruments when subjected to variance analysis by the technique described. The probability falls just below the 0.05 point when the greater variance of JK obtained with the photoelectric instrument was compared with the variance of this segment recorded with the electromagnetic device.

DISCUSSION

The excellent correlation between corresponding IJ and JK segments obtained with each of the direct-recording instruments and with the table suggests that these simple devices record the individual headward and footward movements of the body with an accuracy comparable to that of a stable, well-constructed, high-frequency table. The relatively poor correlations obtained for the JK:IJ ratio, however, indicate that significant differences may exist between the contours of ballistic complexes recorded with the two types of instrumentation, suggesting that qualitative impressions gained from inspection of the two types of records may not always closely coincide.

It is probable that any of the three pickups might be used as advantageously as a ballistocardiographic table in short term experiments involving comparison of individual segment length before and after the introduction of a factor, e.g., a drug to modify cardiovascular performance. It should be emphasized, however, that this statement, based on the correlations, would not hold true when in a given experiment it would be necessary to remove and replace the device between recordings. The varying amplitudes of deflections obtained with repetitive recordings at the same amplification sensitivity also indicate that none of the three devices tested may be used to quantitate initial cardiac force in a manner similar to the method used with a ballistocardiographic table.[8]

If it is possible to devise an instrument which may be accurately and independently standardized and which shows a relatively constant response with variations of placement greater than those encountered in routine use,* it is quite possible that recording of body motion directly may be at least as satisfactory as recording of motion imparted by the body to a table. As the result of these studies it is our feeling that the presence or absence of restraint, restoring force and damping inherent in a table does not significantly modify the individual segments of the ballistocardiogram. If such factors were of great importance, one would expect, in their absence, considerable "overshooting" in the larger segments of a record as compared with the smaller segments. Either such "overshooting" is not present to any significant degree or, if present, it is proportional to the force involved in the formation of the segment. If disproportionate "overshooting" occurred with direct recording it is unlikely that simultaneous segments recorded directly and with the table would show the excellent degree of correlation found in this study. Moreover, it seems unlikely that significant proportionate "overshooting" occurs. If this were present one would expect a significantly greater respiratory variation in IJ and JK segment size with the direct-recording devices than with the table. This was not demonstrated in any subject with any of the three instruments tested.

The statistical results suggest that the three instruments used in this study for direct recording may yield tracings for which normal wave ratio standards could be determined. These ratios would apparently not be unduly influenced by differences in placement of the instrument. It is also possible that standards for a high-frequency table which have been determined for the respiratory varia-

*The calibrated bar-magnet velocity meter recently described by Smith[9] may meet these criteria.

tion of the IJ segment[10] might be applicable to tracings recorded with any of these three devices. To test these possibilities would require careful evaluation with a larger group of individuals than that reported here and would also require study of a group of patients with cardiac abnormalities.

SUMMARY

Normal ballistocardiograms obtained with three types of instruments which record the movement of a cross-bar placed across the shins were compared with tracings simultaneously recorded with a high-frequency table. Statistical studies yielded the following results:

1. A high degree of correlation exists between the IJ and JK segments recorded with the table and the corresponding segments simultaneously recorded with each of the instruments studied.

2. In the case of the JK:IJ ratio, significant correlations between tracings obtained with the table and with each of the direct-recording instruments were not always demonstrated in individual subjects.

3. The variation between the means of the JK:IJ ratio recorded in each of the ten subjects with the three instruments was not significantly different from the variation of the means of corresponding ratios recorded simultaneously with the table.

4. A significant difference could not be demonstrated in the respiration variations of the IJ and JK segments recorded with each of the three direct-recording devices and the respiratory variations recorded with the table.

5. The reproducibility of repeated tracings obtained with the instruments which record body motion directly was in general inferior to the reproducibility of tracings obtained with the table. This finding appeared to be particularly significant in the case of the photoelectric instrument.

The implications of these results, relating to certain theoretical and practical aspects of recording body motion with these devices, are discussed.

The authors are indebted to Miss Mary Jane Tompkins for her assistance in the collection and statistical analysis of the data presented.

The authors wish to express their appreciation to the Sanborn Company, Cambridge, Mass., for the loan of the photoelectric ballistocardiograph, and to the Max Wocher and Son Company, Cincinnati, Ohio, for the loan of the piezoelectric ballistocardiograph.

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TIME RELATIONSHIPS OF BALLISTOCARDIOGRAPHIC MOVEMENTS

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BECAUSE of the many types of ballistocardiographs in use, a wide variety in the timing and configuration of the ballistic waves in normal subjects has been reported.[1,2,4-7,14] Little effort has been made to correlate the ballistic movements with physiologic events, as measured by other methods. For this reason it was felt worth-while to study a large group of normal subjects, in an attempt to determine the normal relationship between the ballistocardiogram and cardiac events.

METHODS

Direct displacement ballistocardiograms were made on ninety young healthy medical students and student nurses. All subjects were questioned and examined as to the possible existence of cardiac or pulmonary disease. Those having a history of rheumatic fever or other cardiac disease and those having any objective findings of cardiac or vascular abnormalities were not included in the series. In this manner, records on eighty-four subjects were selected for study.

All tracings were taken with the subjects lying in sand, using an air conduction system which records displacement ballistocardiograms, as described by Walker and associates.[8] Simultaneous electrocardiograms, heart sounds, carotid and jugular pulses were recorded with the ballistocardiograms, using a Cambridge four-channel direct-writer. The time lag in the recording instruments used was measured and found to be less than 0.01 second.

All tracings were made with the breath held at the end of normal expiration, in order to avoid possible distortion of time relationships by respiratory forces. The tracings were analyzed for timing of the various ballistic and cardiac events. Because of technical difficulties it was not possible to record clear unquestionable heart sounds, carotid, and jugular pulses in all subjects. Therefore, for each group of measurements the entire series of 84 could not be included.

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RESULTS

In this study we have divided, arbitrarily, the ballistic waves into four different groups, for convenience of discussion (Fig. 1). The first group is termed the systolic waves and includes the movements from the H peak to the K nadir. These movements have been shown to occur during the systolic phase of the cardiac cycle.[3,9] The second group is termed the early diastolic waves and consists of the movements from the K nadir to the O nadir. As will be shown, these movements occur primarily during the periods of protodiastole, isometric contraction, and rapid filling. The third group is termed the late diastolic waves

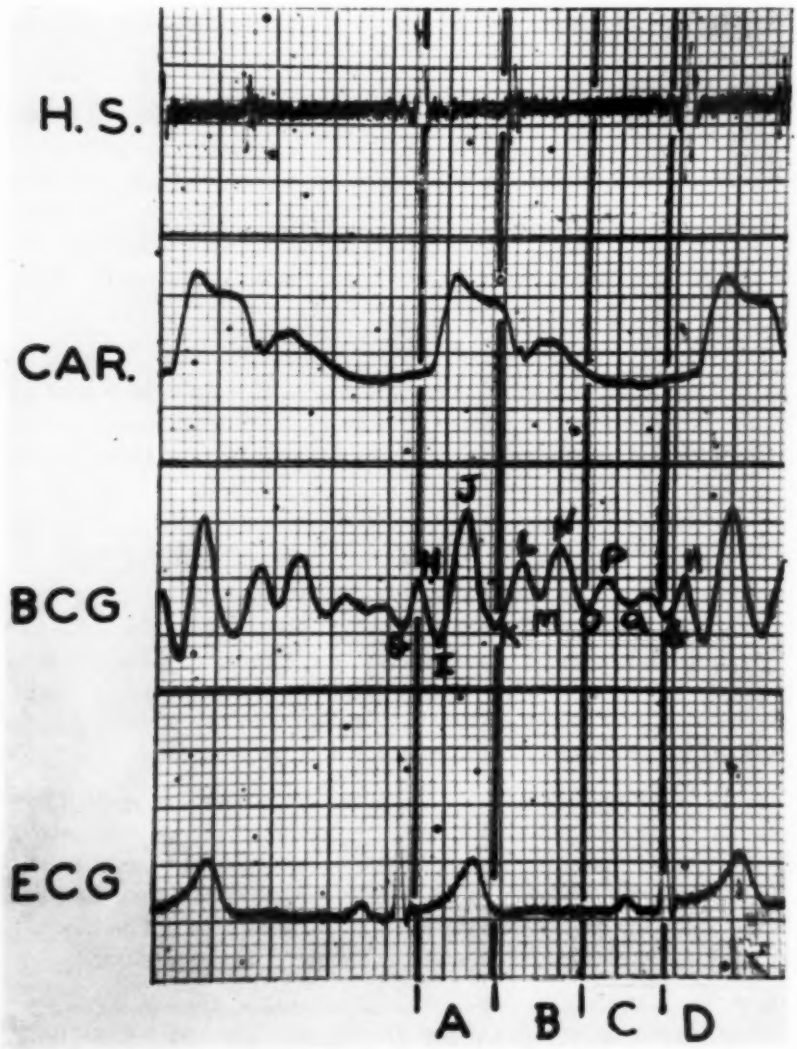


Fig. 1.—Arbitrary divisions of the ballistocardiogram with reference to the cardiac cycle. *A.* The systolic waves (*H-K*). *B.* The early diastolic waves (*K-O*). *C.* The late diastolic waves (*O-G*). *D.* The *G-H* upstroke. [*H. S.*, heart sounds; *CAR*, carotid pulse; *BCG*, ballistocardiogram; *ECG*, electrocardiogram Lead II.]

and includes the movements between the O nadir and the onset of the G-H upstroke of the following cycle. This includes the periods of diastole and a portion of auricular contraction. The G-H upstroke will be discussed separately, since some of the data indicate that this movement occurs not only during the presystolic phase but also during the period of isometric contraction.

It should be emphasized here that the following measurements apply only to tracings made with the displacement technique, using a sand surface. They are not necessarily correct for tracings made with velocity, acceleration, or partially integrated velocity techniques, or for tracings made with other surfaces.

The Systolic Waves.—Starr and associates have postulated that the H-I downstroke is due, at least in part, to recoil from ejection of blood from the ventricles.[9] Study of our data suggests that there may be other factors as well. Theoretically, if H-I is due entirely to recoil, and there is no lag in the carotid pulse, the onset of carotid ejection and the onset of the H-I downstroke should be simultaneous. Actually, there is a measurable physiologic lag between ventricular ejection and the carotid pulse, although to our knowledge this has not been directly measured in man. If we accept the reported values for pulse wave velocity in man as 5 to 30 meters per second[10-12] and allow a distance between the left ventricle and the carotid artery of 20 to 30 cm., the calculated extremes of carotid lag will be 0.007 second and 0.06 second. The observed extremes between H point and the onset of carotid ejection in our tracings are 0.00 and 0.08 second (Table I). As our

TABLE I. TIME RELATIONSHIPS OF THE BALLISTIC MOVEMENTS

	RANGE (SEC.)	MEAN (SEC.)	STANDARD DEVIATION (SEC.)
Q to S_1	0.00 to 0.08	0.043	0.017
S_1 to H	0.00 to 0.10	0.044	0.019
H to carotid ejection	0.00 to 0.08	0.034	0.017
H-K time	0.18 to 0.30	0.237	0.022
S_1 to carotid ejection	0.04 to 0.12	0.075	0.012
K to S_2	−0.07 to +0.04	0.019	0.027
L to carotid incisura	−0.05 to +0.04	0.009	0.021
Jugular V to N	−0.02 to +0.04	0.008	0.015
G to S_1	−0.05 to +0.04	0.002	0.017
Q to G	0.00 to 0.08	0.044	0.019

recording instrument error is about 0.01 second, the lower value would be possible, but the upper value too high. Furthermore, it hardly seems likely that in young healthy adults in a relatively narrow age range, the pulse wave velocity in a given set of vessels could vary as much as 5 to 30 meters per second. We believe that the wide variation in H to ejection time in healthy subjects is evidence that factors other than recoil enter into the genesis of the H-I downstroke. Hamilton and associates have previously suggested this concept.[3]

There is a rough correlation between H to ejection time, and the time between the onset of the first heart sound and the H point. As S_1 to H becomes shorter, H to ejection tends to become longer, and vice versa. In other words,

the H point tends to fluctuate (Fig. 2). This would further suggest that factors occurring during isometric systole, before ejection begins, enter into the genesis of the H-I downstroke.

Starr and associates[9] have shown that the I-J upstroke and the J-K downstroke are related to the impact of blood headward against the arch of the aorta, and then footward against the bifurcation of the aorta and against the peripheral resistance. From our study we have no evidence for or against these concepts. We have merely noted that I-J is the least variable of the ballistic waves.

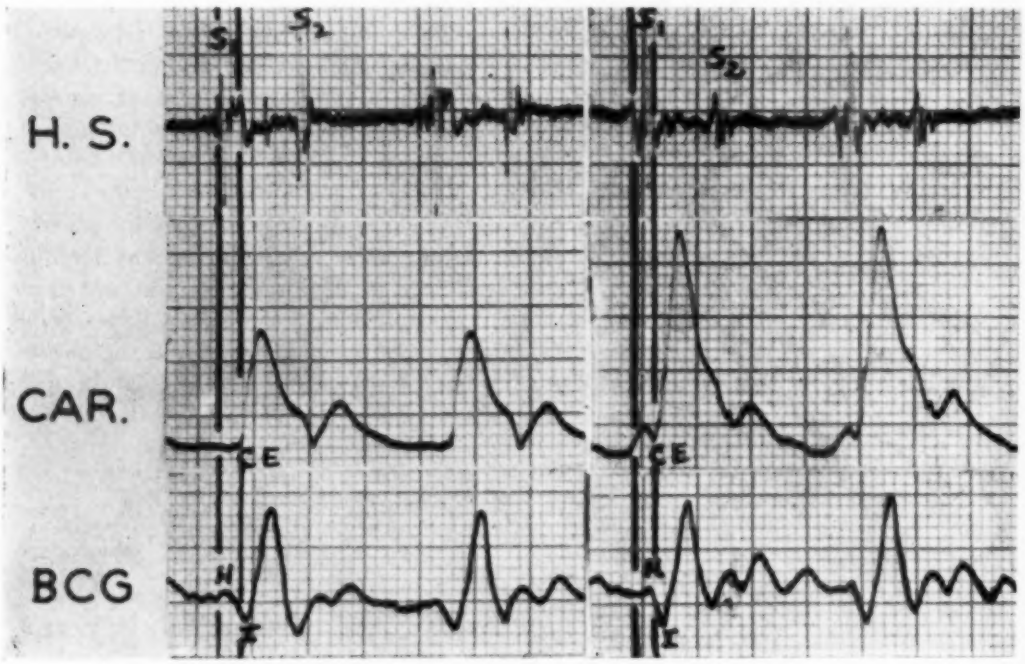


Fig. 2.—Variation in time relations of *H* point in healthy young adults. Vertical lines are drawn through onset of the first heart sound and onset of carotid ejection. Note that in *A*, time from first sound to *H* peak is 0.02 second and time from *H* peak to onset of carotid ejection is 0.06 second; while in subject *B*, S_1-H time is 0.06 second and *H* to ejection time is 0.02 second. Although the total S_1 to ejection time remains relatively the same in these two subjects, the *H* point varies.

In this series the range of values for H-K time is 0.18 to 0.30 second, with a mean of 0.237 and a standard deviation of 0.022 (Table I). It has been found previously by Brown and associates[4] that there is a direct correlation between duration of H-K and body weight. In general, our figures substantiate this trend, but the correlation is not striking.

It can be seen that the H peak occurs between the first heart sound and the onset of carotid ejection. Since we do not know the physiologic lag in the carotid pulse, the exact relationship between the H point and the onset of ventricular ejection cannot be determined. However, it seems likely that the H-I movement begins during the latter part of isometric contraction or near the onset of ventricular ejection.

Early Diastolic Waves.—These waves are the K-L-M-N-O movements and have been frequently referred to as the diastolic waves. This term, however, is not absolutely correct, for these movements do not occur during the long period of diastasis but are most prominent during the phases of cardiac relaxation and early rapid filling. There is much disagreement concerning the genesis of these waves. It has been argued that these movements are mere afterwaves or simple vibratory swings of the body as it rebounds from the strong headward ejection thrust.[2,5] This would seem plausible because of the fact that the frequency of these waves lies within the range of normal body frequency. In addition, there has been noted a wide variety in the timing and configuration of these waves in normal subjects, depending on the recording technique used.

On the other hand, it has been suggested that these diastolic movements are related to active cardiac or circulatory forces. This viewpoint has been strengthened by several observations from our data and from those of others:

1. If these were simple body vibrations, one would expect the waves to diminish gradually in size, each wave being succeeded by a smaller one. However, it has been noted frequently that the second diastolic upstroke (M-N) is as large or even larger than the preceding K-L upstroke (Fig. 1).

2. In certain pathologic conditions the diastolic waves often become quite large, frequently being as large as the I-J upstroke.[4,13]

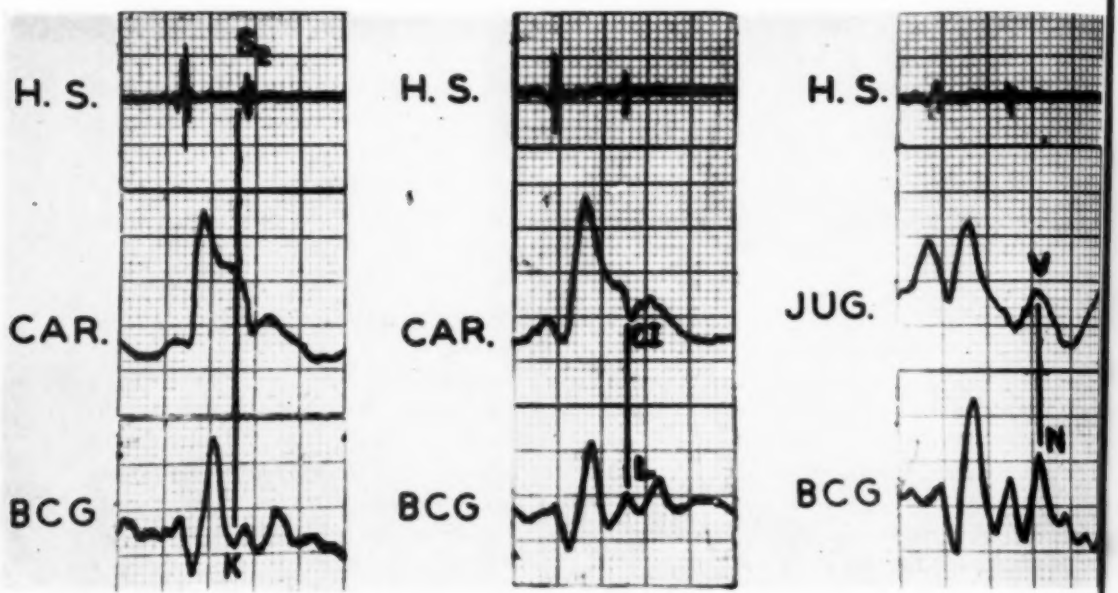
3. It has been noted by Hamilton and associates,[3] and more recently by Tannenbaum and associates,[14] that the L peak tends to occur at the time of the incisura of the arterial pulse. This was believed to indicate that this movement was directly related to some circulatory force and not a simple body oscillation.

In order to show more clearly that these movements are actually the result of physiologic forces, an effort was made to correlate certain ballistic waves with cardiac events.

The first analysis consisted of the measurement of the correlation between the K nadir and the second heart sound. The K to S_2 time was measured in seventy-nine of the eighty-four subjects (Table I and Fig. 3, *A*). The mean K to S_2 time was found to be 0.019 second with a standard deviation of 0.027. Thus it is seen that the K point occurs just prior to the second heart sound and only rarely follows it.

The second measurement concerned the correlation of the L peak with the carotid incisura. For this study the L point to carotid incisura time was measured in seventy-six of the eighty-four subjects. The results are shown in Table I and Fig. 3, *B*. The mean L to carotid incisura time is 0.009 second, with a standard deviation of 0.021. It, therefore, appears that most subjects have an L peak occurring approximately at the time of the carotid incisura, although in this group the mean occurred slightly before the incisura rather than coincidentally with it. Hamilton and associates and Tannenbaum and associates reported that the L peak and the carotid incisura occurred simultaneously,[3,14] but their studies were made using the central arterial pulse rather than carotid tracings. The time lag in the pulse wave between the central pulse and the carotid artery possibly accounts for the earlier occurrence of the L in relation to the incisura which we have noted.

A third analysis was made of the correlation of the ballistic N peak with the jugular V peak. Because of the difficulty in recording jugular pulses, a clear unquestionable V wave could be found in only fifty-eight of the eighty-four subjects. The jugular V to ballistic N time was measured, and the results are shown in Table I and Fig. 3, *C*. The mean V to N time is 0.008 with a standard deviation of 0.015. In nearly one-half the subjects the V and N were coincidental, while in 95 per cent of all subjects the N peak occurred within ±0.03 second of the V wave.



A. *B.* *C.*

Fig. 3.—Time relations of *K*, *L*, and *N* points. *A*. Correlation between *K* point and the second heart sound (S_2). Note that *K* occurs approximately 0.02 second before S_2. *B*. Correlation between *L* point and the carotid incisura (*CI*). *C*. Correlation between the *N* point and the jugular *V* peak.

If these early diastolic waves were simple body vibrations or mere after-waves, one would expect them to vary only with body shape and size and to show no relationship to physiologic events. However, as has been shown, these waves have correlated fairly closely with certain cardiac events—the second heart sound, the carotid incisura, and the jugular V peak. Exact correlations can never occur because of the modifying effect of body vibrations. The fact that the N peak falls within ±0.03 second of the jugular V peak in 95 per cent of a large number of normal subjects would seem to indicate that this wave is primarily due to cardiac forces, with body oscillations playing a secondary role. Apparently, one of the effects of the sand surface is to damp out body oscillations to such an extent that the cardiac forces become predominant in the production of these early diastolic waves.

In order to further verify the relationship between the early diastolic waves and circulatory events, the K to N time was measured and compared to the

heart rate. If these waves are primarily the result of simple body vibrations, there should be no relationship between the length of the K to N time and the heart rate. On the other hand, if these movements are the result of circulatory forces, one would expect the total duration of these waves to become shorter as the heart rate increases. As seen in Table II, this apparently occurs. No apparent correlation was found between the K to N time and body size in this series.

TABLE II. THE INVERSE RELATIONSHIP BETWEEN HEART RATE AND THE K-N TIME

RATE	NO. OF SUBJECTS	AVERAGE K-N TIME (SEC.)
50–59	3	0.217
60–69	19	0.204
70–79	27	0.202
80–89	22	0.193
90–99	5	0.185

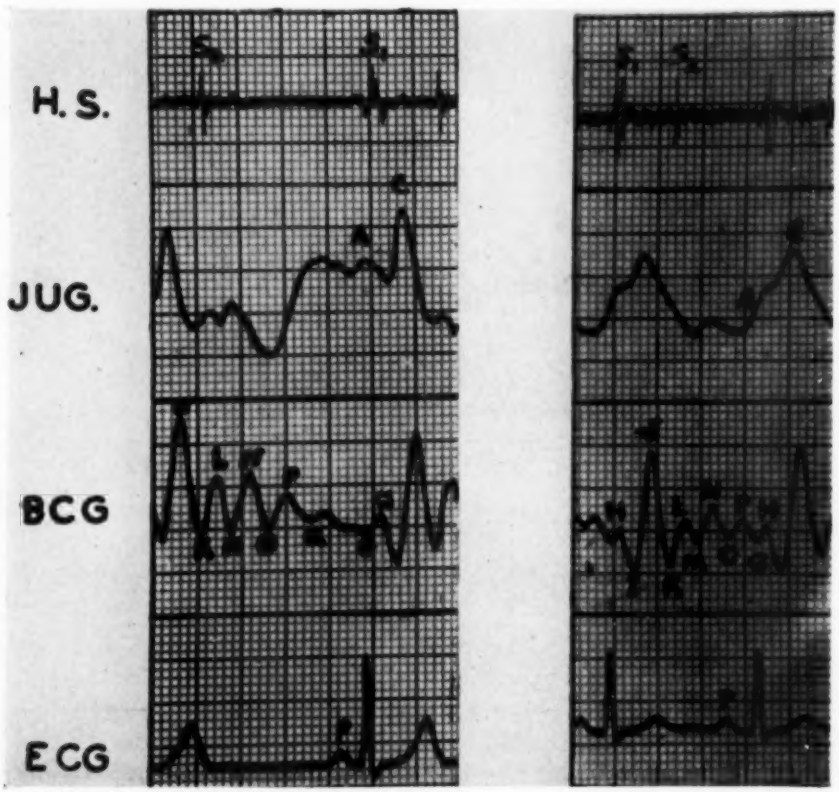
As mentioned, the K nadir usually falls just prior to the second heart sound, and the L peak correlates quite closely with the carotid incisura. Therefore, the K-L upstroke corresponds approximately to the period of protodiastole, as described by Wiggers.[15] Since the N peak occurs with the jugular V peak, it becomes quite apparent that the L-N time corresponds roughly to Wiggers' period of isometric relaxation. The N-O downstroke begins at the peak of the jugular V wave; therefore, the onset of the N-O downstroke corresponds to the onset of rapid filling.

Late Diastolic Waves.—These waves include any movements occurring between the nadir of the N-O downstroke and the onset of the G-H upstroke.

Ballistocardiograms on normal subjects show a variable pattern of small waves, the O-P-Q sequence illustrated in Fig. 1, which are related in time to the diastasic portion of the cardiac cycle. The small diastasic waves vary considerably in amplitude and number but occur in some form in most normal tracings. The number of the waves which are recorded varies directly with the length of diastole. In subjects with slow rates, whose tracings show a clear-cut O-P-Q sequence, it has been noted that the accompanying jugular tracings usually show a temporarily corresponding diastolic wave occurring between the V wave and the A wave. In subjects with rapid rates, this fourth jugular wave is rarely seen, and the O-P-Q sequence is difficult to distinguish from the preceding early diastolic waves or the following auricular contraction waves (Fig. 4).

There is nothing happening in the electrocardiogram or in the heart-sound tracings at this time in the cardiac cycle which can be correlated with these diastasic waves. These waves are undoubtedly influenced by aftervibrations of the body in a manner similar to the early diastolic waves discussed above. However, the known fact that auricular filling is occurring at this time, and the observations that the O-P-Q sequence is related in time to a jugular wave in some subjects, suggests that venous impacts, occasioned by entrance of blood into the auricles from the great veins, may play some role in the genesis of the diastasic waves.

Ballistocardiographic waves occurring during auricular contraction have no consistent pattern and can only be selected by use of simultaneously recorded timing criteria such as the P wave of the electrocardiogram and the jugular A wave. Auricular deflections in subjects with fast rates are difficult to differentiate



A. *B.*

Fig. 4.—The effect of heart rate on the appearance of the late diastolic waves. *A.* Ballistocardiogram on subject with heart rate of 55 per minute, which shows a clear-cut OPQ sequence, as well as an additional wave occurring before the onset of the P wave of the electrocardiogram. Note the close temporal relationship between the OPQ and the large diastolic jugular wave. *B.* Ballistocardiogram on subject with heart rate of 88 per minute, which also shows clear O-P upstroke; but note that it occurs after the P wave of the electrocardiogram begins, so it cannot be as definitely related in time to diastasis as in subject A. The downstroke P-G is related in time to the jugular A upstroke, and is probably due to auricular contraction forces rather than diastasic forces.

absolutely from the preceding O-P-Q sequence (Fig. 4, *B*). In other subjects the auricular deflections appear to impinge on the G-H upstroke. For these reasons auricular waves in the normal ballistocardiogram are important, chiefly, in their effect upon the immediately following G-H upstroke.

G-H Upstroke.—Contrary to most of the other ballistic movements, the G-H upstroke of the normal ballistocardiogram shows several definite variations in configuration. As seen in Fig. 5, these varying patterns can be differentiated into certain definite types, as follows:

1. A sharp upstroke of short duration and small amplitude (Fig. 5, *A*).

2. A rounded upstroke with a more gradual slope and a longer duration than the first type (Fig. 5, *C*).

3. A mixed type which is often notched and sometimes appears to be a combination of the first two types. The mixed type has a longer duration and an earlier onset than either of these (Figs. 5, *D* and 5, *F*).

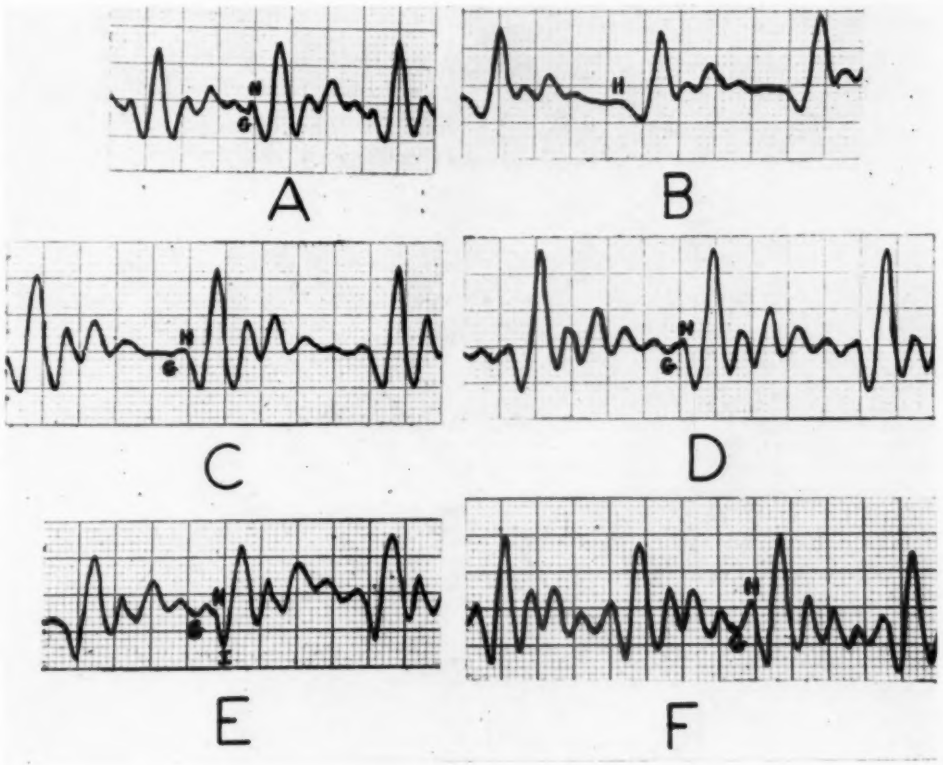


Fig. 5.—Various types of G-H upstrokes seen in normal ballistocardiograms (as discussed in the text). Note that in tracing E the H-I downstroke is notched and prolonged in duration, making it difficult to determine whether the H point is the beginning of the downstroke or is at the notch. With an indefinite H point such as this it is impossible to determine the exact configuration and duration of the G-H.

4. An indefinite type, which sometimes appears to be a double or bifid movement. This type is associated with a rounded, prolonged H-I downstroke that makes it difficult to identify definitely the points G and H (Fig. 4, *E*).

5. Complete absence of G-H (Fig. 5, *B*).

About one-third of our series of eighty-four normal subjects show the Type A G-H (Fig. 5, *A*), about 10 to 12 per cent have no G-H, and the rest show a variety of the types illustrated in Fig. 5.

The duration of all types of the G-H upstroke ranges from 0.02 to 0.08 second, with a mean of 0.042 second. The duration of G-H shows no apparent correlation with body build, sex, or heart rate but does show a rough correlation with the length of the P-R interval (Fig. 6).

In spite of variation in pattern and duration of the G-H, it does show definite time relationships to other physiologic events (Fig. 7). These relationships are as follows:

1. In 67 per cent of the subjects studied, the G-H upstroke begins simultaneously with, or shortly after, the first heart sound, while only 33 per cent begin before the first heart sound.

2. In the great majority of subjects the G-H begins simultaneously with, or after the onset of, the QRS in the electrocardiogram.

3. The G-H upstroke always terminates before the onset of carotid ejection, as determined by simultaneously recorded pulses.

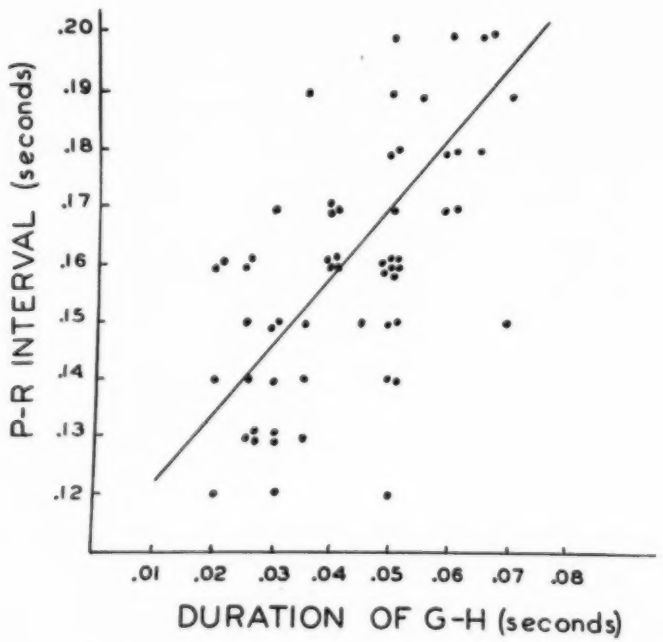
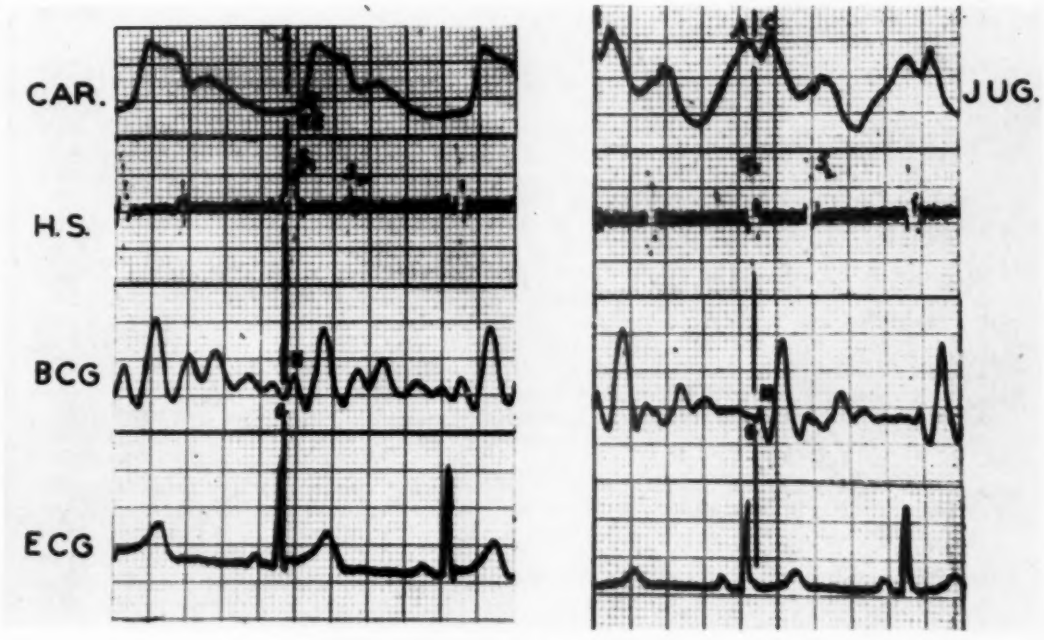


Fig. 6.—Graph showing rough correlation between the duration of G-H upstroke and length of the P-R interval. This correlation suggests that auricular forces play a role in the genesis of the G-H upstroke.

This close relationship of the G-H upstroke to the QRS and to the first heart sound suggests that the genesis of the G-H upstroke is at least partially due to early ventricular activity in isometric contraction. However, it seems reasonable to believe that small movements due to preceding auricular activity can act to mask or accentuate these early ventricular forces, if time between auricular and ventricular contraction is short. Therefore, G-H is related in time both to presystole and isometric contraction.



A. *B.*

Fig. 7.—Time relationships of G-H upstroke to first heart sound, QRS complex of the electrocardiogram, and carotid ejection. Vertical lines are drawn through the onset of the G-H upstroke. Note that in both subjects *A* and *B*, G-H begins after the onset of the QRS complex and terminates before the onset of carotid ejection (CE), although the contour and the duration of the G-H is different in the two subjects. Also note close relation of onset of G-H to the first heart sound (S_1) in both subjects.

SUMMARY

Studies have been made of the time relationships between the ballistocardiographic waves, heart sounds, electrocardiograms, carotid and jugular pulses in a series of normal subjects.

The following observations have been made:

1. A wide variation in temporal relations of the H peak.
2. Close temporal correlation between: (A) the K nadir and the second heart sound; (B) the L peak and the carotid incisura; and (C) the N peak and the jugular V peak.
3. An inverse relationship between the K-N time and the heart rate.
4. The occurrence of one or more waves during the period of diastasis.
5. A wide pattern variation of the G-H upstroke.
6. A temporal relationship of the G-H upstroke to both the presystolic and isometric contraction phases of the cardiac cycle.

These observations suggest certain ideas concerning the genesis of the ballistocardiographic waves. Studies are now in progress to verify some of these concepts and will be reported at a later date.

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INTERPRETATION OF THE VELOCITY MEASUREMENT BALLISTOCARDIOGRAM

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EASE of construction and use have encouraged interest in portable velocity measurement ballistocardiographs. The status of such instruments and their records relative to other types of ballistic systems, the high-frequency undamped machines, low-frequency critically damped machines, and portable displacement recorders, has been summarized recently by Scarborough and associates.[1] A critical examination of the effect of change in network filters on frequency response of electromagnetic recorders has been made[2] and methods for calibrating electromagnetic pickups have been proposed.[3,4] These and other improvements will evolve ultimately a more standardized form of pickup and recording system than is employed now in numerous clinical and laboratory investigations. Variability in criteria for normality of records has been found from laboratory to laboratory. The absence of both standardized recording apparatus and of precise criteria for the normal condition has not delayed, however, the widespread clinical use of these machines. There exists a need for knowledge concerning the diagnostic accuracy of the ballistocardiogram when analyzed by criteria now in use, and when recorded by a popular type coil, network, and filter system. Such information for the Starr table has recently been published.[5] The machine chosen was of the type described by Dock and Taubman,[6] Mandelbaum and Mandelbaum[7] and others, with the impression that the choice of this machine would facilitate comparison of results with those of other workers. The criteria for analysis were chosen because of widespread use and have been published previously by many authors,[5,8] using numerous types of machines. The establishment of more certain normal means and limits for the physical characteristics of such ballistocardiograms was first sought. A sizable group of healthy adults was studied with this as the central objective. A corollary of this analysis was an evaluation of the reliability of these criteria of the ballistocardiogram in indicating a clinically normal cardiovascular system. The work was then extended to include the effect of primarily noncardiovascular disease on the ballistocardiogram and, finally, the effect of serious cardiovascular disease itself.

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MATERIALS AND METHODS

All ballistocardiograms taken during this study were made by a portable electromagnetic ballistocardiographic machine of a construction identical to that of Mandelbaum and Mandelbaum.[7] The recordings were made on a converted General Electric photographic electrocardiograph. All individuals rested on a rigid table for approximately ten minutes prior to registration of the ballistocardiogram and were from 1 to 3 hours postprandial.

A group of 327 normal individuals, men and women, were examined. Their ages ranged from 12 through 65 years (mean 32), with the majority under 30 years of age. This group consisted predominantly of high school and medical school students and professional hospital personnel, all with repeated physical examinations in the past and accurate medical histories. Inclusion in this group was based on a negative history and physical examination, chest roentgenogram, urinalysis in past and present, and the absence of any minor illness at the time of recording the ballistocardiogram.

A second group of seventy-three patients who were hospitalized with relatively severe, diverse, noncardiac diseases were studied, generally at a time when they were convalescing from the severe phases of their illnesses. The ages ranged from 14 to 100 years, averaged 35 years.

The third group studied consisted of 121 cardiac patients who were hospitalized for obvious heart disease and its complications. All in this group had cardiac abnormalities sufficiently severe to warrant hospitalization. The existence of heart disease was further corroborated by means of history, physical examination, teleroentgenogram, electrocardiograms, and cardiac fluoroscopy. Pathology varied and consisted of the following types: congenital, rheumatic (mitral, mitral and aortic, aortic, and mitral, aortic and tricuspid valvular lesions combined), luetic (both aneurysm and aortic regurgitation, together and alone), hypertensive, arteriosclerotic, and cor pulmonale lesions, combined with several miscellaneous causes as myxedema and idiopathic cardiac hypertrophy.

These patients were studied at various times during their course of hospitalization, but, in general, an attempt was made to record the ballistocardiogram at the time cardiac failure had improved as much as could be expected. A total of 136 ballistocardiograms were taken on these 121 patients. No selection or exclusion of patients was made on the basis of factors now thought to influence the ballistocardiograms (such as bundle branch block). The group was one containing individuals with severe heart disease of many types.

All tracings were subjected to the following analysis: (1) classification on the basis of the criteria of Brown, Hoffman and de Lalla;[8a] (2) measurement in millimeters of the depth of K and the height of J with subsequent calculation of JK:IJ ratio; (3) measurement to the nearest 0.01 second of the time interval from the apex of H to the nadir of the K wave in all cycles; (4) detection of the maximum variation between H:K interval in all cycles.

TABLE I. SUMMARY OF BALLISTOCARDIOGRAPHIC FINDINGS

GROUP	TOTAL NUMBER OF CASES	CLASSIFICATION OF RECORDS (BROWN, HOFFMAN AND DE LALLA)						RATIO OF JK:IJ			H-K TIME INTERVAL				
		0	1	2	3	4	UNCERTAIN	MAX.	MIN.	MEAN	DURATION IN SECONDS			VARIATION BETWEEN STROKES MEAN	NUMBER OF GRAPHS WITH NO VARIATION
											MAX.	MIN.	MEAN		
Normal persons	327	271	20	13	11	3	9	8.0	0.62	1.7	0.40	0.10	0.245	0.01	107
Individuals with noncardiac disease	73	31	8	7	12	13	2	2.6	0.9	1.6	0.26	0.15	0.206	0.01	26
Individuals with cardiac disease	121	41	8	10	25	37	0	4.0	0.9	1.96	0.36	0.17	0.223	0.015	31

RESULTS

Normal Group.—Analysis of the tracings of this group on the basis of the criteria of variation in magnitude and form of the tracing (Brown, Hoffman and de Lalla)[8a] yielded the following results: 271 records, Grade 0; twenty records, Grade 1 (slight variation); thirteen records, Grade 2 (moderate variation); eleven records classified as Grade 3 (marked variation); and three records were Grade 4 because the variation was so marked that systolic complexes could not be distinguished from diastolic components. In nine records artifacts, tremor, body motion, or amplitude variation so extreme that the tracing was not fully recorded, prevented classification.

The relationship of K depth to J height expressed as a ratio had a mean value for the entire group of 1.7. The maximum ratio was 8.0 and the minimum was 0.6. It was noted that 94 per cent of the group had ratios between 1.1 and 2.3, or within 0.6 of the mean value of 1.7.

The mean of the duration of time from the nadir of H to the nadir of K was 0.245 second, and the range of the group was from 0.1 to 0.40 second. In any given individual tracing the variation in this H-K interval from cycle to cycle was too small to be measured in 107 tracings. The remaining records in which there were a sufficient number of identifiable ballistic cycles for comparison (121) revealed an average variation of 0.01 second and ranged from 0.0 to 0.07 second. Ninety-nine tracings possessed a sufficient number of bizarre cycles in the recorded strip of film so that a comparison between H-K times was meaningless.

Individuals Convalescing From Serious Noncardiac Disease.—Applying the same four methods of analysis to this group of seventy-three individuals showed thirty-one records classified Grade 0; eight, Grade 1; seven, Grade 2; twelve, Grade 3; and thirteen, Grade 4. The mean of the JK:IJ ratio was 1.6 and the range of variation was from 0.9 to 2.6. The average H-K time interval was 0.206 second and ranged from 0.26 to 0.15 second. The variation in H-K time from cycle to cycle in the same graph was insignificant in twenty-six cases, and averaged 0.01 second in the remainder, with a maximum of 0.09 second.

Individuals With Clinically Obvious Heart Disease.—Analysis of this group of 121 patients revealed forty-one records classified Grade 0; eight, Grade 1; ten, Grade 2; twenty-five, Grade 3; and thirty-seven, Grade 4. The mean JK:IJ ratio was 1.96 and the ratio varied from 0.9 to 4.0. The H-K time interval averaged 0.22 second, with a range of 0.17 to 0.36. The H-K time could not be measured in seventy-two graphs because of the large number of bizarre complexes. Variation of the H-K time in individual graphs was insignificant in thirty-one cases and, in the remainder, averaged 0.15 second with a maximum variation of 0.6 second.

A further breakdown of the group of cardiac patients was made according to the etiologic classification, as determined by available means, of the underlying heart disease. In the study of the records by the classification of Brown and associates[8a] the etiologic groups of cor pulmonale, congenital, and miscellaneous types contained too small a number of patients to be accurate. In the rheumatic, luetic, hypertensive, and arteriosclerotic groups, normal as well as all

four grades of variation were present with no significant distribution. The JK:IJ ratio in the luetic group and in the hypertensive group was 2.6 and 2.2, respectively. These are substantially greater than that for the group of normal patients and exceed the ratio in the other cardiac groups. Two of the luetic patients had a JK:IJ ratio of 1.6, while nine hypertensive patients had similar ratios. Although examples of early and late M complexes were seen in all three groups, the precise criteria for determining these forms were not available and thus no statistical study could be made.

DISCUSSION

Ballistocardiography offers a potentially new method of gathering information about the cardiovascular status of individuals. The value of the information gained rests upon knowledge of normal distribution and physiologic variations. Five constituents of the ballistocardiograph were considered in the interpretation of the record obtained by a portable nonstandardized machine. These were: (1) forms of individual complexes, (2) degree of variation in regularity and definitiveness, (3) ratio of JK to IJ, (4) duration of H-K time, and (5) the variation in the H-K interval in a series of cycles.

The appearance of several different complex forms, such as early M and late M, has been described.[1,9] Easily recognizable examples of these waves were seen in the present series in all three groups. Attempts to determine the criteria or ratios necessary for designation of such waves were unsuccessful. The number of classical examples of each was too small in this series of over 500, and the number of borderline cases too great for criteria to be drawn.

Variation in IJ amplitude with respiration and of complex regularity and definitiveness has been used in classifying graphs. Insofar as the present series of 327 normal persons of diverse ages (mean 32 years) is a representative sample, it appears that an appreciable (14 per cent) percentage of such individuals will have a definite variation in IJ height and complex regularity, that is, will have graphs classified as 1, 2, 3, or 4. This is in keeping with the incidence of 25.2 per cent obtained by Scarborough and associates[5] in a study of normal persons with an older mean age of 44. The higher incidence of abnormal wave form in older age groups is well substantiated and is probably responsible for this higher figure. There was an inverse relation between the degree of variation and the number of people having this variation; only three persons with normal cardiovascular systems by the criteria used had 100 per cent bizarre complexes. The incidence of definite variation in the group of individuals with noncardiac disease increased to 54 per cent. This emphasizes the role of extracardiac factors in producing ballistocardiographic abnormality.

While 66 per cent (80 out of 121) of the individuals with frank cardiac disease had graphs with some degree of variation (1, 2, 3, or 4), only 31 per cent of the individuals had 100 per cent variation or completely bizarre, Grade 4, graphs. Furthermore, 55 per cent of the individuals who were convalescing from noncardiac disease also had ballistocardiograms graded 1, 2, 3, or 4, and 18 per cent of this same group were Grade 4. These results emphasize that abnormality of the ballistocardiogram was not necessarily associated with cardiac disease. Since

34 per cent of the persons with frankly diseased hearts had normal records, the determination of the presence or absence of heart disease on the basis of the ballistocardiogram was difficult.

The JK:IJ ratio of normal persons as recorded on a Starr or Nickerson table is about 1.0.[5] Smith and Bryan,[11] using a low-frequency velocity measurement ballistocardiograph, obtained a ratio of approximately 1.3 in a study of 100 normal people between 20 and 30 years of age. Barrera and associates[12] have previously called attention to this observation that records obtained with the electromagnetic machines have a greater JK:IJ ratio than those from the Starr or Nickerson table. Results of the present study of a larger group of individuals and of a greater age range confirm this; the mean JK:IJ ratio of normal persons was 1.7, and there were numerous examples of ratios of 2.0 and 3.0 with an extreme of 8.0. These figures are substantially greater than the limits of 0.85 to 1.40 set by Scarborough for the Starr-type machine. The presence of noncardiac or diverse types of cardiac disease produced no change in the average JK:IJ ratio or in the extremes observed. The one exception to this was seen within the group of cardiac patients. The persons with hypertensive and luetic heart disease had higher average values for the ratio. This observation is in keeping with previous reports on such patients.[1,13] Certain individual cases of these two types, however, had a normal JK:IJ ratio. The hypertensive and luetic group thus overlapped all other groups, giving a high JK:IJ ratio limited in diagnostic value. This lack of specificity of a high JK:IJ ratio has previously been noted.[1] It has been produced by certain drugs[14] and is accentuated by use of the electromagnetic machines.

The present results confirm the observation that the H-K time of an individual is constant to about 0.01 second,[10] and that there is a relatively great (fourfold) variation between different persons. The presence of either cardiac or noncardiac disease did not affect the mean H-K time, its extremes, or its variation in the individual.

SUMMARY

1. A portable electromagnetic ballistocardiograph was used to study three groups of individuals: normal persons, patients confined to a hospital and convalescing from noncardiac disease, and patients with obvious cardiac disease.

2. The records were analyzed by four methods: (a) presence of so-called early M or late M pattern, (b) JK:IJ ratio, (c) H-K time interval and its variation, (d) Brown, Hoffman, and de Lalla criteria.

3. Precise determination of the limits of the early and late M patterns could not be made.

4. Observations that the JK:IJ ratio is materially increased by use of the electromagnetic machine are confirmed.

5. The JK:IJ ratio and the H-K interval and its variation failed to distinguish the three groups. Within the cardiac group those with hypertensive and luetic heart disease had a higher JK:IJ ratio, but some of these individuals had normal ratios.

6. Records with some degree of variation (1, 2, 3, or 4) were found in 66 per cent of the individuals with frank cardiac disease, in 55 per cent of the patients convalescing from noncardiac disease, and in 14 per cent of the normal persons. Grade 4 ballistocardiograms were found in 31 per cent, 18 per cent, and 0.9 per cent of these three groups, respectively. These results emphasize that abnormality of the ballistocardiogram was not necessarily associated with cardiac disease.

7. It is emphasized that 34 per cent of the individuals with frank heart disease had normal ballistocardiograms.

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LEFT AURICULAR PRESSURE CURVE BEFORE AND DURING FIRST DEGREE ATRIOVENTRICULAR BLOCK

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STOCKHOLM, SWEDEN

IN CASES with mitral stenosis and sinus rhythm the auricular contraction will result in a more pronounced pressure peak than normal in the left auricular pressure curve.

In normal cases the auricular contraction has been considered responsible only for 20 to 25 per cent of the ventricular filling. In experimental work on dogs Hirschfelder[2] found that with an increasing degree of mitral stenosis there was an increasing importance of the auricular contraction in the ventricular filling. In severe stenosis, however, an absence of auricular systole was encountered.

The left auricular mean pressure is considerably elevated in cases with mitral stenosis. It is, therefore, difficult to estimate the increased amount of ventricular filling due to the more forceful auricular systole in these cases.

In this communication we want to present a patient with mitral stenosis in whom a left auricular pressure curve was obtained before and after the production of a first degree atrioventricular block.

METHOD

The left auricle was punctured from the right side, the needle being introduced paravertebrally above the ninth rib according to Björk. Cardioangiography suggested by Crafoord was performed and about 60 ml. of contrast medium was injected in the left auricle in less than two seconds, resulting in an atrioventricular block of first degree, i.e., the atrioventricular conduction time increased from 0.16 second before the injection to a maximum of 0.29 second immediately after the injection. Some minutes later the atrioventricular time was normal again.

CASE REPORT

A 35-year-old woman had a valvular lesion diagnosed at the age of seven. Since 1945, she has shown increasing dyspnea on exertion, in 1948 symptoms of heart failure developed, and she is now a complete invalid.

From the Sabbatsberg Hospital, Surgeon-in-Chief, Professor Clarence Crafoord.
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Physical examination indicated no thrills, but there was a low-pitched rumbling diastolic murmur with a presystolic crescendo accentuation ending in a sharp first heart sound. There was also a soft systolic murmur. Both murmurs were heard over the apex area. The second heart sound was accentuated over the pulmonary artery. Sinus rhythm was regular; heart rate, 105 per minute. Roentgenogram showed a heart volume of 760 ml. corresponding to 430 ml. per square meter of body surface with an enlarged left auricle. An electrocardiogram was quite normal with an atrioventricular time of 0.16 second. The electrokymographic record was similar to that in mitral stenosis. The left auricular pressure curve (see Fig. 1) shows peaks *1, 2, 3* due to the auricular contraction. The pressure peak *4* corresponds to the closure of the mitral valves.

The left auricular pressure curve about two minutes after the cardioangiography shows an atrioventricular time of 0.26 to 0.29 second (see Fig. 2). Due to the prolonged atrioventricular time the pressure peaks, *2* and *4*, are completely separated. Then peak *2* is found more prominent than peak *4*. The pressure values in mm. Hg for the different points are given in Table I.

TABLE I

POINTS ON THE RECORD	PRESSURES IN MM. HG	
	BEFORE A-V BLOCK	AFTER A-V BLOCK
1	12.1	21.1
2	21.9	30.4
3	20.7	19.1
4	21.4	23.2
5	13.8	20.1
7	16.7	24.8
Mean	16.8	23.6

Pressure measurements in the left auricle before and after the production of a first degree atrioventricular block in a case of mitral stenosis. 1, 2, 3—auricular systole; 4—closure of the bicuspid valves; 4, 5—the rapid descent of the ventricular base; 7—the opening of the bicuspid valves. (6—the closure of the aortic valves at the beginning of the second heart sound. Phonocardiogram was not obtainable.) A-V, atrioventricular block.

DISCUSSION

When the atrioventricular conduction time is normal the two pressure peaks 2 and 4 do interfere with each other. Therefore, it is impossible to decide whether the pressure fall between points 2 and 5 predominantly might be due to a pressure fall between points 2 and 3 or between points 4 and 5. The pressure fall 4 to 5 (the descent of the ventricular base) was 7.6 mm. Hg or 45 per cent of the mean pressure in the left auricle when peaks 2 and 4 are superimposed. After separation of the two peaks (2 and 4) by increasing the atrioventricular conduction time from 0.16 to 0.29 second, the pressure fall between points 2 and 3 is excluded. The pressure fall remaining for the systolic descent of the atrioventricular valvular plane (points 4 to 5) is then only 3.1 mm. Hg or 13 per cent of the mean auricular pressure. Thus peak 2 was found much more prominent than peak 4 in this case with mitral stenosis. It is assumed that the pumping mechanism of the heart is not altered by the increased atrioventricular conduction time. The findings do not permit any conclusions about the corresponding pressure relations in healthy subjects.

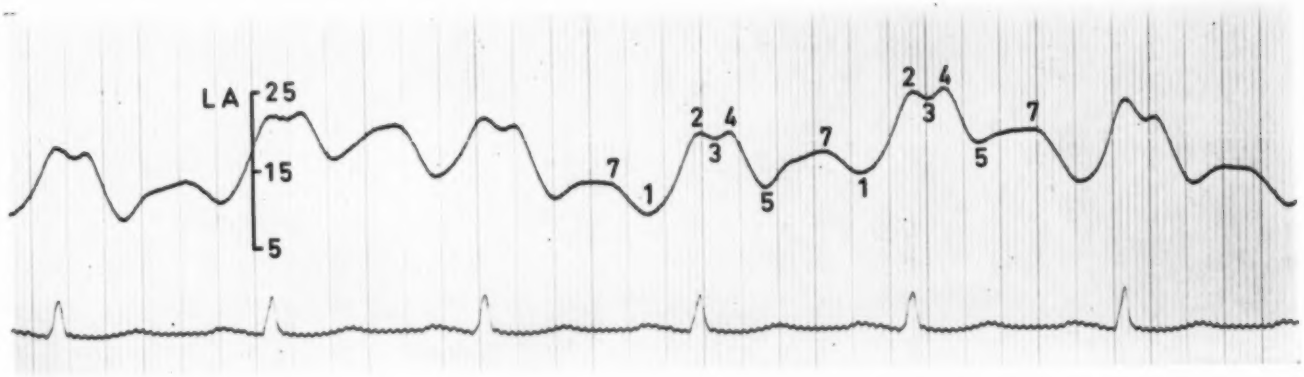

Fig. 1.—Left auricular pressure curve in a case of mitral stenosis. The atrioventricular conduction time, 0.16 second. *1, 2, 3*—the auricular contraction. Peak *4* (closure of the mitral valves) is superimposed on Peak *2*. *4, 5*—descent of the ventricular base (pressure fall, 7.6 mm. Hg). *7*—opening of the mitral valves.

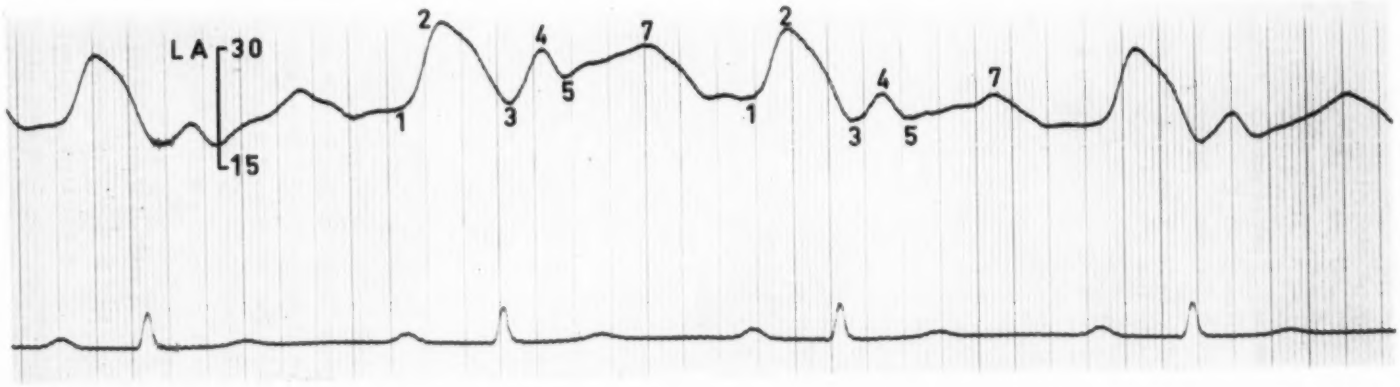

Fig. 2.—Left auricular pressure curve in the same case after production of a first degree atrioventricular block. The atrioventricular conduction time, 0.26 to 0.29 second. Peaks *2* (auricular contraction) and *4* (closure of the mitral valves) are separated. *4, 5*—descent of the valvular plane (pressure fall, 3.1 mm. Hg). *7*—opening of the mitral valves.

SUMMARY

The left auricular pressure curve was recorded through a needle inserted into the left auricle in a case of mitral stenosis with regular sinus rhythm. After the injection of contrast medium into the auricle a transient prolongation of the atrioventricular conduction time appeared. This event made it possible to study the auricular contraction pressure peak without interference with the pressure waves caused by the closure of the atrioventricular valve and the systolic downward movement of the atrioventricular plane.

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CLINICAL AND HEMODYNAMIC FEATURES OF UNCOMPLICATED INTERATRIAL DEFECT IN ADULTS

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IT HAS been known for many years that functioning communications between the atria may ultimately lead to serious disability and death in the human being.[1] More recently, the technique of cardiac catheterization has removed some of the diagnostic uncertainty that was formerly associated with such defects and has also thrown considerable light on their hemodynamic effect.[2,3] With the possibility that some interatrial defects can be closed surgically comes the need for an even better understanding of the functional implications of the anomaly. In the hope of obtaining additional information on some of these matters, it seemed appropriate to examine the clinical and catheterization data on a group of adult patients in which the diagnosis of interatrial defect, uncomplicated by other congenital anomalies, was reasonably certain.

MATERIAL AND METHOD

Nineteen adult patients with interatrial defects as diagnosed by cardiac catheterization form the basis for the study. Sixteen of the patients were drawn from the case material at the Variety Club Heart Hospital and three from that at the Minneapolis Veterans Hospital. There were ten men and nine women in the group, the ages ranging from 17 to 51.

The technique of cardiac catheterization was carried out in the usual manner. The existence of a functioning communication between the atria was thought probable if the oxygen content of the right atrial blood exceeded that of blood from the innominate vein or superior vena cava by 2.0 volumes per cent. The average difference between the 2 points in the series was 4.4 ± 1.7 volumes per cent (Table 1). The catheter was passed through the interatrial defect in five cases. As pointed out by Cosby and associates,[4] diagnostic criteria of this type do not rule out anomalous pulmonary venous drainage (into the right atrium), nor, for that matter, does passage of the catheter through the defect into the left atrium, since the two anomalies may conceivably coexist. Anomalous pulmonary venous drainage, however, is a relatively rare congenital anomaly and, when pres-

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ent, frequently gives characteristic roentgenologic findings. Such findings were not present in any of the cases in the present series, and it seems reasonable to assume that all the patients included had interatrial defects.

TABLE I. OXYGEN CONTENT OF BLOOD SAMPLES TAKEN FROM VARIOUS SITES AND FEMORAL ARTERIAL SATURATION

CASE NO.	O_2 CONTENT, VOLUME PER CENT					FEMORAL ARTERY SATURATION (%)
	SVC	RA	RV	PA	FA	
1	13.8	22.1	—	19.0	22.1	—
2	14.7	19.4	—	19.1	21.3	97
3*	18.0	—	22.4	22.4	24.5†	—
4	10.2	15.2	—	15.7	17.0	93
5†	13.1	17.3	—	—	18.3	91
6	12.2	15.8	15.9	16.1	18.5	100
7	10.8	14.5	14.5	15.2	16.0	97
8	12.6	15.8	15.8	15.6	17.9	98
9	10.6	14.6	14.6	14.5	16.6	95
10	16.1	20.9	21.2	21.3	22.5	100
11*	10.8	13.1	13.8	13.6	16.6†	—
12	10.1	16.1	—	15.6	16.9	95
13	13.8	18.1	18.0	17.8	18.7	97
14*	8.8	15.4	13.3	12.8	15.6†	—
15	15.2	19.3	18.7	19.0	20.3	94
16*	9.5	12.5	11.9	11.9	14.4	97
17	14.3	19.8	19.8	20.8	22.4	94
18	14.5	17.5	—	16.2	17.7	97
19	14.9	16.9	18.1	17.6	19.6	95
Mean	12.8	16.9	16.8	16.9	18.8	96.0
S.D.	2.4	2.6	3.1	2.9	2.7	7.6

*Catheter passed through defect

†Pulmonary venous sample

For the calculation of the systemic flow, the oxygen contents of superior and of inferior vena cavas were averaged if values for both were available.[5] The arteriovenous oxygen difference was then determined by subtracting this average value from the oxygen content of the femoral arterial blood. When no inferior caval samples were available, the oxygen content of mixed venous blood was estimated by adding 1.0 volume per cent to the oxygen content of blood from the superior vena cava or innominate vein, since Dexter and associates' figures,[6] as well as our own, indicate that normally there is an oxygen difference of about 2.0 volumes per cent between samples taken from superior and from inferior vena cavas.

The pulmonary arterial flow was calculated by subtracting the oxygen content of pulmonary arterial blood from that of femoral arterial blood. The oxygen consumption was then divided by the resulting atrioventricular oxygen difference in the usual manner. As Hickam points out,[7] a more accurate value for pulmonary flow can be obtained by using the pulmonary venous oxygen content, thus obtaining the true pulmonary arteriovenous oxygen difference. Use of blood

from the femoral artery, instead of from the pulmonary vein, leads to an overestimation of the pulmonary flow, particularly if there is a significant right-to-left shunt. By judging from the femoral arterial oxygen saturation in the present series, such a shunt was recognizable in only one of the cases. Recalculation of the pulmonary arterial flow, using estimated values for pulmonary venous oxygen content, did not materially alter the average flow for the group, although there were some discrepancies in individual cases.

Left-to-right shunts were estimated by subtracting systemic flows from pulmonary arterial flows, and, like the latter, probably tend to be somewhat overestimated in some cases.

Mean pressures were determined by planimetric integration of pressure tracings as recorded optically or directly by Hamilton manometric or strain gauge systems. Atrial pressure data were not utilized, since many of the atrial pressure curves were so unsatisfactory as to defy accurate analysis.

In order to rule out additional congenital cardiac defects, blood samples and pressure tracings from the right ventricle and pulmonary artery were carefully examined. The pulmonary artery was entered in all but one of the patients in the study. In this case (Case 5), the catheter entered a huge chamber, thought to be a common atrium, and could not be advanced further. In a second case (Case 6), the pulmonary arterial pressure tracing was lost but at the time of catheterization showed no evidence of pulmonary stenosis.

Pulmonary resistance, as such, was not calculated. Right ventricular pressure work was calculated from the equation

$$W = 60Q \times R\ (.0135), \text{ where}$$

W is work in kg.-m./hr.,
Q is pulmonary blood flow in liters per minute, and
R is right ventricular mean systolic pressure.

The right ventricular mean systolic pressure was used instead of the right ventricular mean pressure, as given in Table II, since right ventricular work is expended during systolic ejection.[8] The value is obtained by drawing a line through the right ventricular pressure tracing at the pulmonary arterial diastolic pressure level (Fig. 1). Parallel lines are then dropped to the base line from the point where the pulmonary diastolic line crosses the ascending and descending limbs of the right ventricular pressure tracing. The area thus enclosed is measured with a planimeter and is divided by its base which is approximately equal to the duration of ventricular ejection. Values obtained in this manner are from one and one-half to two times larger than the corresponding values for right ventricular mean pressure but the two values usually parallel each other fairly closely ($r = 0.9$), if the pressure waves are faithfully recorded. The regression equation obtained from our data was:

$$\text{RV systolic Pm} = 2.73 + 1.57 \times \text{RV Pm}.$$

Estimation of the systolic mean pressure in this way involves the assumption that the reference point for the values so obtained is zero (atmospheric) pressure.

TABLE II. SYSTEMIC AND PULMONARY FLOWS, MEAN PRESSURES IN PULMONARY ARTERY AND RIGHT VENTRICLE, AND RIGHT VENTRICULAR PRESSURE WORK

CASE	FLOW L./MIN.		L-R SHUNT L./MIN.	MEAN PRESS. MM. HG		RV PRESSURE WORK KG./M. PER HR.	QRS AXIS, DEGREES PLUS
	SYST.	PULM.		PA	RV		
1.	3.3	7.3	4.0	40.3	24.3	171.5	99
2.	4.5	11.5	7.0	15.5	11.6	211.5	92
3.	6.4	16.8	10.4	11.7	8.6	204.1	RBBB
4.	4.7	20.4	15.7	28.9	21.8	697.3	106
5.	6.4	29.0	22.6	—	—	—	RBBB
6.	6.1	13.6	7.5	—	—	—	95
7.	4.8	25.1	20.3	21.5	16.7	589.6	96
8.	5.1	10.5	5.4	24.7	15.8	283.2	112
9.	5.3	15.1	9.8	14.9	13.5	223.8	108
10.	5.9	26.3	20.4	12.6	8.2	441.0	124
11.	4.5	7.2	2.7	12.2	9.2	89.8	90
12.	4.3	19.1	14.8	28.6	25.3	699.3	RBBB
13.	4.3	19.8	15.5	11.0	8.5	243.8	110
14.	4.2	8.7	4.5	18.6	15.8	174.1	—
15.	6.6	20.9	14.3	22.6	16.1	535.0	RBBB
16.	6.8	10.6	3.8	14.2	12.7	140.8	96
17.	3.6	15.7	12.1	18.0	12.2	344.6	126
18.	8.4	19.6	11.2	41.0	26.2	787.5	73
19.	7.9	14.6	6.7	20.9	17.8	306.3	RBBB
Mean	5.4	16.4	11.0	21.0	15.6	361.0	102.1
S. D.	1.4	6.2	5.9	9.0	5.7	215.0	13.7

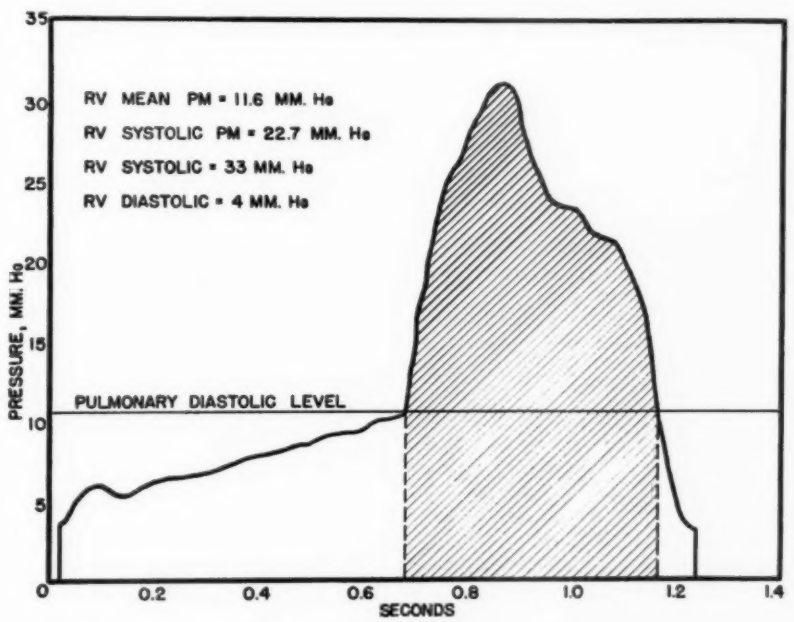

Fig. 1.—Right ventricular pressure curve. Diagram showing the method of obtaining right ventricular mean systolic pressure. The shaded area is used for the calculation of mean systolic pressure.

Since right ventricular diastolic pressure, in the compensated heart, is at or near zero, the assumption is probably justified. A more accurate value, however, can be obtained by subtracting the mean diastolic from the mean systolic pressure, especially if the right ventricular diastolic pressure is elevated.

CLINICAL FEATURES

Clinical data are set out in Tables III and IV. The presence of heart disease was detected during the first few years of life in three of the nineteen cases. In seven it became apparent in mid- or late childhood (age 7 to 14) or during adolescence. In the remaining eight cases it was discovered at age 18 or later. The

TABLE III. FIRST INDICATIONS AND PRESENTING COMPLAINTS IN PATIENTS WITH INTERATRIAL SEPTAL DEFECTS

CASE	AGE	SEX	FIRST INDICATION AND AGE	MAIN COMPLAINT ON ADMISSION
1.	37	M	Murmur, 25	Shortness of breath
2.	19	M	Murmur since birth	None
3.	34	M	Substernal pain, 32	Pain around heart
4.	26	F	Murmur, 12	Shortness of breath
5.	21	M	Enlarged heart, 9	Shortness of breath
6.	19	F	Precordial aching, 14	Shortness of breath
7.	23	F	Murmur, 7	Pain around heart
8.	17	M	Murmur, 1	None
9.	24	F	Murmur, 13	Palpitation
10.	23	M	Murmur, 16	Palpitation
11.	20	F	?	?
12.	19	F	Murmur, 2	Shortness of breath
13.	24	F	Abnormal X-ray, 18	Pain around heart
14.	30	F	?	?
15.	33	M	Murmur, 11	Pain around heart
16.	34	F	Abnormal X-ray, 23	Palpitation
17.	22	M	Murmur, 22	Fainting episode
18.	51	M	Dyspnea, 25	Shortness of breath
19.	30	M	Enlarged heart, 25	Pain around heart

presence of systolic murmurs was the most frequent abnormality that suggested the presence of heart disease (10 cases). Shortness of breath was the most frequent complaint on admission, and in two cases (1 and 5) it was almost totally incapacitating. Five patients were concerned chiefly with pains in the region of the heart and, in one of these, the description of the pain suggested true angina pectoris (Case 3). In two other patients precordial pain was present but was overshadowed by shortness of breath. Palpitation (3 cases) was identified electrocardiographically in one case as supraventricular. Two patients had no complaints of any type.

Seventeen patients had systolic murmurs, one had no murmur, and in one case no information was available. All of the systolic murmurs were relatively prominent, as judged by the grading, and most were maximal at or near the pulmonic area. One, however, was best heard at the apex. Basal systolic thrills accompanied the murmurs in nine cases. In three instances, high-pitched diastolic

murmurs were heard along the left sternal margin, and in two others such murmurs were thought to be present by some observers. Low-pitched apical diastolic murmurs were heard in two cases and may have been present in one additional case. In one instance the murmur was prominent enough to suggest the diagnosis of mitral stenosis as the sole lesion present. In the other two, a diagnosis of Lutembacher's disease was made. Definite accentuation of the pulmonic second sound was present in ten of the cases and slight accentuation in six. Accentuation was often accompanied by duplication (7 cases). Clubbing of the digits, cyanosis, pulmonary râles, and peripheral edema were absent in all the patients at the time of examination. In two cases, however, there was a history of intermittent mild peripheral edema, and several gave vague stories of mild cyanosis on exertion.

TABLE IV. MURMURS AND THRILLS DETECTED IN NINETEEN PATIENTS WITH INTERATRIAL DEFECTS

	SYSTOLIC			DIASTOLIC		P_2
CASE	GRADE	MAX. INTENSITY	THRILL	PITCH	MAXIMUM	
1.	None	—	None	None	—	+ + +
2.	II	2 LIS	None	None	—	—
3.	III	3 LIS	None	None	—	+ +
4.	III	4 LIS	+	Low	Apex	+ +
5.	IV	Apex	+	High	LSM	+ +
6.	III	2 LIS	None	High	2 LIS	+ +
7.	III	2 LIS	+	None	—	+ +
8.	III	2 LIS	+	High	LSM	+
9.	IV	2 LIS	+	Low	Apex	+ +
10.	III	4 LIS	+	None	—	+
11.	IV	3 LIS	+	None	—	+
12.	IV	2 LIS	+	Low	Apex	+ +
13.	III	2 LIS	None	High	2 LIS	+ +
14.	—	—	—	—	—	—
15.	III	3 LIS	None	None	—	+ +
16.	III	2 LIS	None	High	2 LIS	+
17.	III	2 LIS	+	None	—	+
18.	III	3 LIS	None	High	LSM	—
19.	III	3 LIS	None	None	—	+

LIS—left intercostal space; LSM—left sternal margin.

FLOW AND PRESSURE

The mean resting systemic flow in the series was normal. The mean resting pulmonic flow, however, was 16.4 ± 6.2 liters per minute, or over 3 times normal. The mean left-to-right shunt, as calculated, was about twice as large as the systemic flow. If one accepts 18 mm. Hg as the upper limit of normal for pulmonary arterial mean pressure, pulmonary hypertension was present in nine of the cases and was moderately severe in two of them. Severe pulmonary hypertension, such as occurs in Eisenmenger's complex, for example, was not found. Attempts to correlate pulmonary flow with pulmonary arterial pressure, however, met with failure.

Calculation of pulmonary resistance was not attempted but it is clear, from perusal of the flow and pressure data, that resistance was reduced in all but one case (Case 1).

WORK OF THE RIGHT VENTRICLE

The most inclusive and meaningful expression of the burden on the heart produced by a left-to-right shunt is the calculation of the excess work done by the right ventricle under these circumstances. Since, in the present material, right ventricular and pulmonary mean pressures were available, as was the pulmonary flow, the potential energy, or pressure work, done by the right ventricle could be estimated. Some difficulty arose, however, in the choice of the correct mean pressure to use in the calculation. Prec and associates[9] used the average pulmonary arterial pressure (systolic plus diastolic divided by 2) and obtained a mean value of 1387 gm.-cm./beat, or 58 kg.-m./hr., in six normal subjects (Table V). By using the integrated pulmonary arterial mean pressure,

TABLE V. PRESSURE WORK OF THE RIGHT VENTRICLE IN NORMAL SUBJECTS AND IN PATIENTS WITH INTERATRIAL SEPTAL DEFECTS

TYPE OF PRESSURE USED		KG.–M./HR.		GM.–CM./BEAT	
		MEAN	S. D.	MEAN	S. D.
Pulmonary mean	Normal*	58	18	1387	517
	IASD	269	152	5541	3307
R. V. mean	IASD	205	120	4191	2524
R. V. systolic mean	Normal†	105	—	2362	—
	IASD	361	215	7550	4997

*From Prec and associates[9]

†From Handelsman and associates[11]

IASD—Interatrial septal defect

the corresponding values for patients with interatrial defects are 5,541 and 269, respectively. As pointed out by Frank[8] and by Remington and Hamilton,[10] it is probably more accurate to employ the right ventricular mean systolic pressure for calculation of right ventricular pressure work. In the present material, this procedure yields values of 7,550 gm.-cm./beat, or 361 kg.-m./hr. Satisfactory normal values calculated in this way do not seem to be available. By using the data for one hypothetical normal subject provided by Handelsman and associates,[11] a value of 105 kg.-m./hr. was obtained. The right ventricular mean systolic pressure was calculated from their right ventricular mean pressure by the use of the regression equation derived from our own data. If this single estimate is indicative of the approximate normal value, all but two of the cases

in the present series showed definite increase in right ventricular pressure work, and in three of them it was more than six times normal.

The importance of kinetic, or velocity, work in patients of this sort is undoubtedly great. The data necessary for its calculation, however, were lacking. The method used by Prec and associates could not be applied because no figures for the cross-sectional areas of the pulmonary arteries were available. It is generally recognized, however, that kinetic work is directly related to the third power of flow, while the relation between pressure work and flow is a linear one.[12] Some idea of the relative magnitude of kinetic work in the present material can, therefore, be derived from the data at hand. The ratio pulmonic flow/systemic flow, when raised to the third power, serves as an index to right ventricular kinetic work, although it gives no indication as to its absolute magnitude. In the normal subject the value for the cubed ratio is one. In the present material, the average value for the ratio was 41.1, the range being from 8.7 to 143. The calculation of right ventricular kinetic work in patients with interatrial defects would, therefore, materially increase estimates of total right ventricular work.

Even if it were possible to calculate kinetic work, as well as pressure work, the result would still be incomplete. The energy dissipated as a result of turbulent flow would in no way be represented. Some degree of turbulence in the right ventricle and pulmonary artery probably exists even in the normal subject.[9] In patients with interatrial defects the presence of turbulence can hardly be questioned and the characteristic basal systolic murmur is, in all likelihood, a manifestation of it. Basal systolic thrills, present in nine of the nineteen cases studied, provide even more impressive external evidence of it.

THE FRONTAL PLANE QRS AXIS

Calculation of frontal plane mean QRS vectors gave values of +90 degrees or more in all but one of the patients who did not show right bundle branch block. The average value was +102.1 degrees. In the patients with right bundle branch block, it seems likely that the prolongation of the QRS interval (0.12 sec., or more) was due to ventricular hypertrophy rather than to damage to the bundle branch itself. The presence of abnormal ventricular gradients in the five cases supports this view. Also, the group probably tended to show higher pulmonary flows than did the patients without bundle branch block, although the difference between the 2 means was not statistically significant. In the single electrocardiogram that showed a frontal plane QRS axis of +73, there was a wide, shallow S wave in limb Lead I, suggesting that the true axis lay to the right of the calculated one.

Neither pulmonary flow nor right ventricular pressure work was significantly correlated with the frontal plane QRS axis if the cases of right bundle branch block were omitted. If one can assume that the latter actually represent cases with QRS axes that are far to the right and arbitrarily assigns each of them a value of +130 degrees, the correlation coefficients (flow vs. axis, and work vs. axis) become barely significant. It seems likely, therefore, that such a relation-

ship does, in fact, exist but that it is obscured by the difficulty in calculating numerical axes in cases exhibiting right bundle branch block.*

DISCUSSION

From the clinical point of view, the material is similar to that reported previously. It is of interest that many patients with interatrial septal defects go for many years without developing symptoms and that the first symptom to make its appearance is usually dyspnea on exertion.[13] The frequency of precordial pain, which has received attention before,[14] is also notable. The latter symptom may, of course, be a manifestation of cardiovascular neurosis engendered by the knowledge that a congenital cardiac lesion is present. It is also possible that it represents a sign of myocardial ischemia, itself the result of massive hypertrophy of the right ventricle. Proof of these speculations, however, is not forthcoming.

The occurrence of a prominent systolic murmur, maximal in the pulmonic area, is one of the traditional diagnostic criteria for interatrial defect. Somewhat less well known is the frequency with which systolic thrills accompany the murmurs. It becomes apparent, therefore, that distinguishing between interatrial defects and other congenital lesions may at times be difficult or impossible without cardiac catheterization. There is a very real possibility, for example, of confusing interatrial defect with isolated pulmonic valvular stenosis unless catheterization data are available. Cardiovascular fluoroscopy, although usually helpful, does not always resolve the difficulty. The explanation for the systolic murmur and thrill probably has to do with the increase in pulmonary flow, usually in the presence of dilatation of the pulmonary artery. An attempt to establish the point by relating the intensity of the murmur with the size of the pulmonary flow was disappointing, probably because of the large subjective element in clinical grading of the murmurs.

The diastolic murmurs sometimes found in patients with interatrial defect cause considerable confusion. High-pitched diastolic murmurs in the pulmonic area are presumably associated with pulmonary hypertension or with deformity of the pulmonary valve accompanying the interatrial defect, possibilities which our data neither confirm nor deny. The presence of an apical rumbling diastolic murmur suggests the coexistence of mitral stenosis (Lutembacher's[15] syndrome). In this connection, the theory that patients with interatrial defect are more likely to develop mitral stenosis than are normal individuals seems to rest on questionable evidence of the sort provided by Roesler.[1] It seems possible, in cases of marked right ventricular hypertrophy, that low-pitched apical sounds or murmurs may be generated in the right side of the heart, rather than in the left side. In Case 4, the initial diagnosis of mitral stenosis, on the basis of a

*The mean QRS axes were determined in the horizontal plane in six patients, under the guidance of Dr. James Dahl, using the spatial vector analyzer described by Simonson and associates.[20] One of the axes was normal (−49°). The others had moved to the right and anteriorly, in a counterclockwise direction, one as much as 270 degrees. This directional change was confirmed by use of the stereovectorcardiographic technique of Schmitt.[21] It was found that the mean horizontal QRS axis is closely related to pressure work of the right ventricle and that this relationship seems considerably better than the relation between the mean frontal QRS axis and right ventricular pressure work.

rumbling diastolic murmur, was rejected when no left atrial enlargement could be found and when catheterization disclosed the presence of a large left-to-right shunt through an interatrial defect. A similar case, recently called to our attention (but not included in the series) was subjected to exploration as a candidate for mitral commissurotomy. Although the clinical evaluation was in the hands of highly competent observers, a perfectly normal mitral valve was found at operation.[16] It cannot be denied, of course, that mitral stenosis and interatrial defect may coexist, but it has yet to be established with finality that the association is anything more than fortuitous. In any event, it seems wisest to interpret low-pitched apical diastolic sounds and murmurs with caution when they are found in patients with interatrial communications of functional significance.

In spite of the presence of dyspnea on exertion in most of the patients studied, the average resting systemic blood flow was normal. This substantiates the clinical impression that dyspnea in patients with interatrial defect is not necessarily a manifestation of cardiac failure in the usual sense and may, in fact, precede the development of failure by many years. It also disproves the notion that the systemic circulation is deprived of blood because of the increase in pulmonary flow.[1,17] Until failure supervenes in a patient with the anomaly, there is no reason to expect the systemic flow to be lower than normal.

The absence of cyanosis and of marked femoral arterial oxygen unsaturation at rest may be taken to mean that in the presence of uncomplicated interatrial defect marked right-to-left shunting is unusual. When cardiac failure occurs, however, such shunting undoubtedly takes place. In the presence of a common atrium, some shunting of venous blood into the systemic circulation is to be expected, as probably occurred in Case 5. In addition, the coexistence of a complicating congenital anomaly may produce a significant right-to-left flow through the interatrial defect as probably occurred in some of the cases reported by Cosby and associates.[4] Marked degrees of arterial unsaturation in patients thought to have interatrial defect and who are not in failure should, therefore, bring to mind the possibility that the diagnosis is incorrect or incomplete.

The absence of a significant relation between pulmonary flow and pressure comes as no surprise. Comparatively low pulmonary arterial pressures may accompany very large pulmonary flows with correspondingly low values for pulmonary resistance. The opposite is also true. That increase in pulmonary flow over the space of many years may lead finally to increase in pulmonary resistance and, possibly, to pulmonary arteriosclerosis seems very likely. This was probably the situation in Case 1, where the pulmonary flow was small but the mean pressure quite high. It seems likely that at one time the patient had a large pulmonary flow and a comparatively low pressure. It was decided elsewhere that because the patient was totally disabled by his disease, operative closure of the defect should be attempted. Preoperative catheterization, done over a year after our own observations were made, showed that virtually no left-to-right shunt was present and that the pulmonary arterial pressure remained high. Unfortunately, the patient succumbed postoperatively and at autopsy an interatrial defect measuring 3 x 2.5 cm. was found. There was marked right ventricular hypertrophy and pronounced dilatation and arteriosclerosis of the

pulmonary artery and its major branches.[18] Similar anatomic changes in patients with interatrial defect have been described before.[19] Their exact significance and their mode of development cannot be determined until long-range studies by modern methods are available on patients such as the one described. In addition, it should be borne in mind that the present studies represent the situations that prevailed when the patients were at rest. That the size of the shunt and the relation between pulmonary flow and pulmonary arterial pressure may change during exercise has been demonstrated in a small series of patients by Hickam.[7] Similar studies on larger groups of patients, repeated at intervals during the course of the disease, will no doubt provide answers to many of the questions that are apparent but not answerable on the basis of data collected under resting conditions.

The development of surgical means of treating interatrial defects obviously represents an important step forward. The tremendous load under which the right ventricle must labor in some patients with such defects is made clear by the present study. The outlook in such patients is undoubtedly poor; and, even though operative techniques for closing interatrial defects are not yet entirely satisfactory, it seems appropriate to apply them without delay in selected cases with large defects. As the technique is improved and the mortality lowered, all patients with functioning interatrial communications that can be shown to increase the work of the right ventricle significantly may become candidates for the procedure. The situation may thus become somewhat comparable to that now prevailing with regard to patent ductus arteriosus, except that the threat of bacterial endocarditis is much less grave in patients with interatrial defects. At the present time, therefore, the most suitable candidates for attempts at surgical closure are those with no complicating lesions but with large left-to-right shunts, definite evidence of right ventricular hypertrophy, and some degree of physical incapacity. In the future, it may become advisable to operate on patients with smaller shunts even though there is no definite right ventricular hypertrophy or incapacity. It should not be forgotten, however, that some patients with small defects and small shunts never develop symptoms and live out normal life spans. Careful evaluation, in the individual case, of the effect of the defect on the right ventricle should provide some basis for deciding whether or not to attempt surgical closure.

CONCLUSIONS

1. Functioning interatrial communications may exist for many years without producing symptoms. In almost one-half (8 of 19) of the cases studied, the defect was undetected before the age 18.

2. Prominent systolic murmurs, usually basal, are frequently, but not always, present. Thrills accompanying the murmurs are not uncommon and may cause diagnostic confusion.

3. The pulmonary arterial flow is often markedly increased but may be only slightly so. Slight to moderate pulmonary arterial hypertension is a frequent finding, but severe elevation of pulmonary arterial pressure is probably rare. There is apparently no relation between flow and pressure in the pulmonary

arterial system in patients with the anomaly, but pulmonary vascular resistance is probably low in most patients with the defect.

4. Right ventricular pressure work is increased usually and sometimes markedly so. Kinetic work also is increased significantly although its absolute value is difficult to determine.

5. The frontal plane QRS vector is usually +90 degrees or more in patients with significant interatrial defects, and right bundle branch block is not uncommon. Some relation between pulmonary flow and frontal plane QRS vector probably exists but could not be established definitely in the study reported.

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A COMPARATIVE ANALYSIS OF THE ECCENTRIC DOUBLE-LAYER REPRESENTATION OF THE HUMAN HEART

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MANY electrocardiographers have approximated the distribution of current generators in the human heart by a single equivalent current dipole located in a fixed position in the heart and changing its orientation and strength during the heart beat. Heretofore, this approximation has been based strongly on the assumption that the distance from the point on the body, where an electrode is placed, to the heart is very large in comparison with the dimensions of the electrically active portions of the heart. The dipole approximation, which has been adopted almost universally in view of its simplicity, permits the use of such concepts as the heart vector and the geometric representation of limb-lead voltages as vector dot-products. It is a basic concept in the rapidly expanding field of vectorcardiography. Also, it lies at the root of clinical analyses of limb-lead data in terms of such quantities as the mean electric axis and the ventricular gradient. Clearly, the dipole representation of the heart has received wide use and, at least reluctant, acceptance. Yet the errors in this approximation have not been established quantitatively and unequivocally.

The electrical aspects of the heart and body were represented in simplest version by Einthoven and associates,[1] who proposed a dipole (to represent the heart) located in a homogeneous plane conducting lamina of infinite extent (to represent the body). Even such a simple representation can be very useful, if applied cautiously, in fostering an understanding of certain aspects of the electrocardiogram. Similar results were subsequently obtained by placing the heart dipole at the center of a homogeneous circular lamina[2] and at the center of a homogeneous conducting sphere.[3] A refinement of these representations has been made by removing the unrealistic restriction that the heart dipole be located at the center of the sphere.[4] In this paper, a further step is taken by replacing the eccentric dipole by a distributed double-layer current source which is believed to be a more accurate representation of the electrical properties of the heart. The results based upon this last representation are useful in obtaining a quantitative estimate of one of the errors inherent in eccentric dipole theory; namely,

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the discrepancy between the potential produced by an eccentric current double layer and that produced by a current dipole of equal strength and eccentricity.

DOUBLE-LAYER REPRESENTATION OF THE HEART

In seeking an electrical representation of the heart that is more realistic than a dipole, it is necessary to consider the distribution of current generators in the heart. The polarized membrane theory of heart muscle is widely accepted today; moreover, the manner in which the heart is excited electrically and the approximate sequence with which the wave of depolarization spreads through the myocardium have been partially established. While information is far from complete on this subject, there is enough evidence for the present purpose to make a reasonable estimate of the electrical conditions that exist during the inscription of the QRS complex to which this analysis is confined.

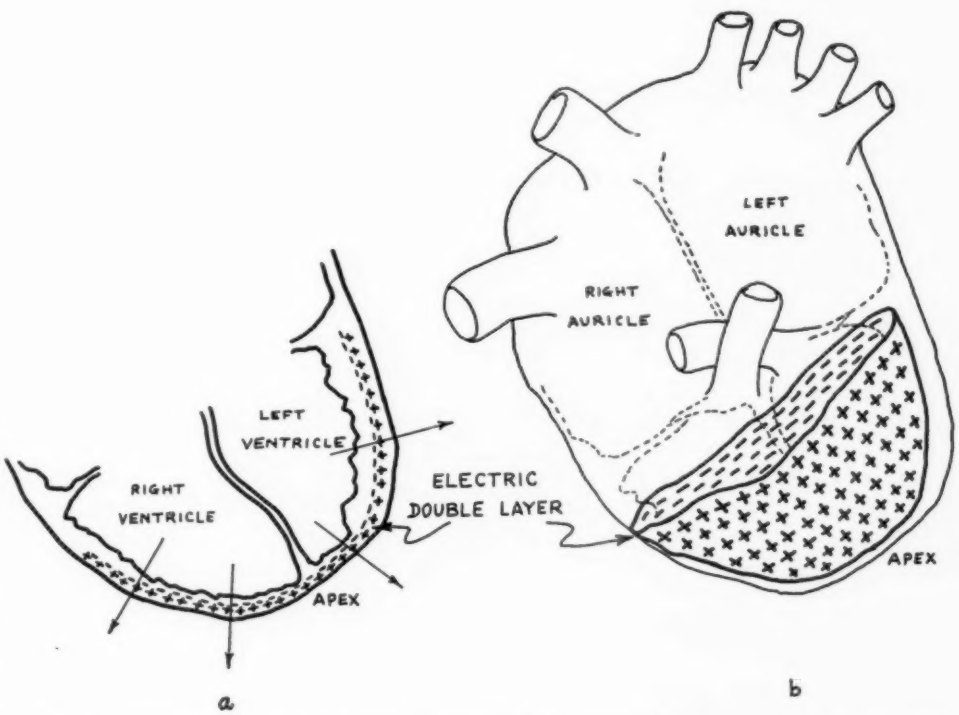

Fig. 1.—Cross-sectional (*a*) and three-dimensional (*b*) schematic representation of the electric double-layer wave of depolarization in the myocardium during the inscription of the QRS complex.

The wave of depolarization at a given instant of time during QRS is shown schematically in Fig. 1, *a* which portrays a cross-section view of the myocardium. This representation, admittedly a simplification of the actual conditions, is the usual one that is discussed in books on the subject.[5] As time progresses, the double layer shown travels outward through the myocardium, disappearing last from the left side which is considerably thicker than the right. The three-

dimensional view of Fig. 1, *b* suggests that the double-layer shape is approximately a portion of a spherical surface and that the rim of the double layer forms, roughly, a circle.

For the purposes of this analysis it is desirable to devise an approximate representation of the electric double layer in the myocardium that is not too complex and yet one which does not depart from the actual double layer to as great an extent as does the dipole. Consequently, for rough analysis of the problem, it is assumed that:

(1) The double-layer rim is a circle of radius c.
(2) The double layer is uniform.

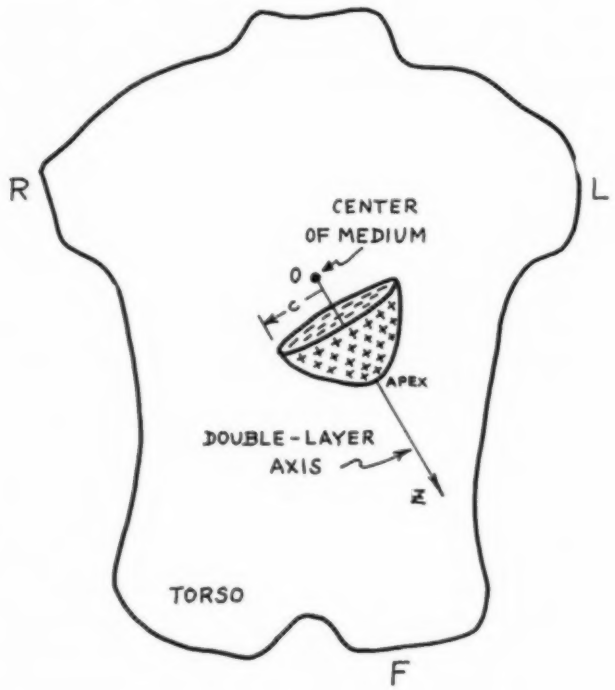

Fig. 2.—Approximate representation of the ventricular depolarization wave of the human heart which embodies the assumptions that the double layer is uniform with a circular rim of radius c and with an axis passing through the center O of the medium.

(3) The axis of the double layer (a line through the center of and perpendicular to the circle of radius c) passes through the center 0 of the medium. These assumptions are portrayed in Fig. 2. The first two assumptions have been used elsewhere[6] with a third requirement of a centric double layer, which is more restrictive than the case treated here, but quantitative conclusions were not drawn for the case of a finite medium.

It is desirable to point out some of the limitations of these assumptions before proceeding, in order to emphasize that the results of the analysis should be used with caution. The circular edge assumption (1) is obviously not fulfilled at every instant of time since the myocardium is not precisely a portion of a

sphere. Moreover, even if the myocardium were a spherical surface, the rim of the double layer would not necessarily be a circle since this also depends upon the thickness of the walls as well as the rate at which the depolarization wave passes through the walls.

It is essential to assume a uniform double layer (2) in order to avoid extreme complexity in the analysis. It is quite unlikely that the double layer is uniform, although this has been assumed by others, but the degree of nonuniformity cannot be estimated from information now available.

Assumption (3) is rarely fulfilled, but it has been introduced primarily because it represents an orientation of the double layer which results in the largest departures from the dipole approximation, as can be shown by calculations, and, therefore, gives the worst cases that might be encountered in practice. In addition, it leads to some analytical simplifications as compared with the case of a double layer whose axis does not pass through the center of the medium.

With the assumptions regarding the heart as a current generator established, it remains to adopt the assumptions that have been customarily employed concerning the medium and skin boundary. Therefore, it is assumed that:

(4) The medium is homogeneous, isotropic, and resistive.

(5) The torso is spherical in shape.

Various conflicting aspects of these last assumptions have been discussed by many others.[7,8] The application to electrocardiography of the results of the analysis are, of course, limited by the degree to which these assumptions apply to the human subject.

ANALYSIS AND RESULTS

The representation of the heart and body which incorporates all of the stated assumptions is given in Fig. 3. An analysis of this system is carried out in Appendix I, which utilizes the fact that the potential produced by the double layer is the same as that which would be produced by a circular double-layer disc of the same total moment which coincides with the rim of the given double layer. The expression for the potential V at any point on the surface of the conducting sphere is shown to be

$$V = \frac{p}{4\pi\gamma R^2} \sum_{n=1}^{\infty} \frac{2(2n+1)}{n(n+1)} \left(\frac{h}{R}\right)^{n-1} P_n'\left(\frac{b}{h}\right) P_n(\cos\Theta) \qquad (1)$$

where

p = double-layer total moment
γ = conductivity of the homogeneous medium
R = sphere radius
Θ = polar angle measured from the double-layer axis
c = radius of circular rim of the double layer
b = distance from the center of the circular rim to the center 0 of the sphere
$h = (b^2 + c^2)^{\frac{1}{2}}$
$P_n(\cos\Theta)$ = Legendre polynomial of degree n
$P_n'(b/h)$ = first derivative of the n^{th} degree Legendre polynomial $P_n(b/h)$ with respect to b/h.

The case of a dipole can be extracted from Equation (1) by imposing the condition of zero radius of the double layer. With $c = 0$, $h = b$ and $P_n'(1) = \frac{1}{2}n(n+1)$. Thus,

$$V_d = \frac{p}{4\pi\gamma R^2} \sum_{n=1}^{\infty} (2n+1) \left(\frac{b}{R}\right)^{n-1} P_n (\cos \Theta) \qquad (2)$$

where V_d is the potential produced by a dipole, located at the center of the circular disc of radius c, which has the same moment as that of the double layer and whose axis also passes through the sphere origin 0.*

The first two terms of Equation (1) and Equation (2) are identical as can be seen by writing them out explicitly. Since the difference between Equation (2)

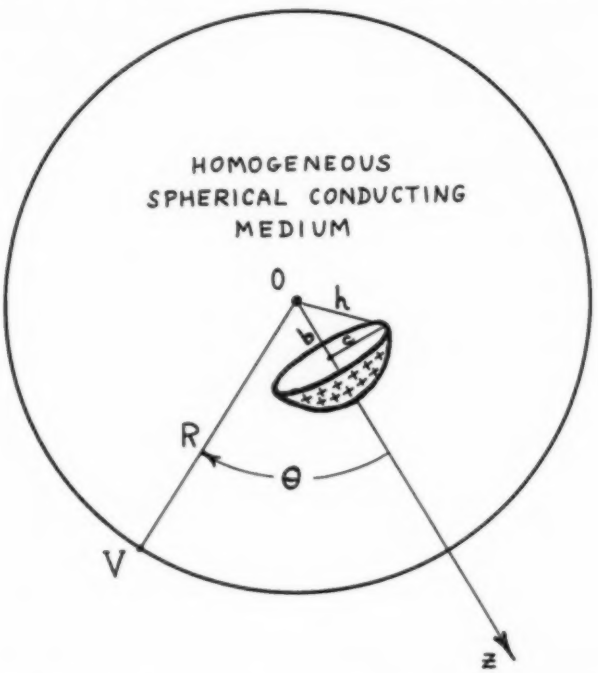

Fig. 3.—The dome-shaped double layer of Fig. 2 immersed in a homogeneous, spherical conducting medium of radius R. The double-layer rim is a circle of radius c whose center is eccentric by the distance b from the sphere center O; $h^2 = c^2 + b^2$. A point of potential V on the sphere boundary is located by the angle Θ measured from the double-layer axis.

and Equation (1) is of principal interest, these two terms will cancel upon subtraction resulting in

$$V_d - V = \frac{p}{4\pi\gamma R^2} \sum_{n=3}^{\infty} (2n+1) \left[\left(\frac{b}{R}\right)^{n-1} - \frac{2}{n(n+1)} \left(\frac{h}{R}\right)^{n-1} P_n'\left(\frac{b}{h}\right)\right] P_n (\cos \Theta). \qquad (3)$$

*The closed-form expression[4,9] corresponding to Equation (2) is

$$V_d = \frac{p}{4\pi\gamma R^2 f} \left[\frac{1 - f^2}{(1 + f^2 - 2f \cos \Theta)^{3/2}} - 1\right]$$

where $f = b/R$.

The fact that the first two terms cancel indicates that the difference given by Equation (3) will be very small for small values of b/R and c/R. However, the series in Equation (3) does not converge rapidly for larger eccentricities and radii approaching 0.4R and it is necessary to use values of n up to approximately 10. The most convenient form of Equation (3) for computation purposes is obtained by carrying out the differentiation of $P_n(b/h)$ which enables the difference to be expressed entirely in terms of c/R, b/R and $P_n(\cos \Theta)$.

Computations of the difference given in Equation (3) and of the dipole potential given in Equation (2) were performed for $0 \leqq c \leqq 0.4R$, $0 \leqq b \leqq 0.4R$ and $0 \leqq \Theta \leqq 180°$. A comparison between the dipole and double-layer potentials can be made from Fig. 4 for the largest eccentricity and double-layer radius considered, $b = 0.4R$ and $c = 0.4R$. The potential has been normalized by taking $3p/4\pi\gamma R^2 = 1.0$ in these curves. The boundary potential produced by a centric dipole is given also for comparison with the eccentric results. It can be seen that the largest departures between the dipole and double-layer potentials occur in the vicinity of $\Theta = 0$, but that the two curves are very nearly coincident for Θ larger than 20°. This same trend is displayed for less eccentricity and smaller double-layer radii. It is also significant to note that the departures between the centric and eccentric dipole are much more pronounced than those between an eccentric dipole and an equally eccentric double layer.

It is possible to describe the difference between the dipole and double-layer potentials in greater detail than shown in Fig. 4 by defining the following per cent difference:

$$\text{Per cent difference} = \frac{(V_d - V)\ 100}{V_{d_{max}}} \tag{4}$$

where $V_{d_{max}}$ is the maximum value of V_d, which occurs at $\Theta = 0$.*
This definition tends to de-emphasize, to some extent, the per cent error in regions where V or V_d are small in comparison with $V_{d_{max}}$. However, it does give a faithful picture in the vicinity of $\Theta = 0$, which is the region of most importance, and has the virtue of avoiding infinite values. This would not be the case if the difference V_d-V were expressed in the more conventional manner as a percentage of V or V_d.

A typical family of curves of the per cent difference is given in Fig. 5 for the largest double-layer radius considered, $c = 0.4R$. For smaller values of c the results are similar in behavior but the per cent differences become uniformly smaller as c approaches zero. It is very significant that the per cent difference displays a sharp peak in the vicinity of $\Theta = 0$. Indeed, for $18° \leqq \Theta \leqq 180°$ which represents 97.5 per cent of the surface of the sphere, it can be seen in Fig. 5 that the per cent difference is always less than that for the centric case at $\Theta = 0$ for all values of b between 0 and 0.4R. This is also true for smaller values of c.

*$V_{d_{max}}$ is very simply expressed in closed form by setting $\cos \Theta = 1$ in the closed-form expression for V_d. The result is

$$V_{d_{max}} = \frac{p}{4\pi\gamma R^2} \frac{(3 - f)}{(1 - f)^2}$$

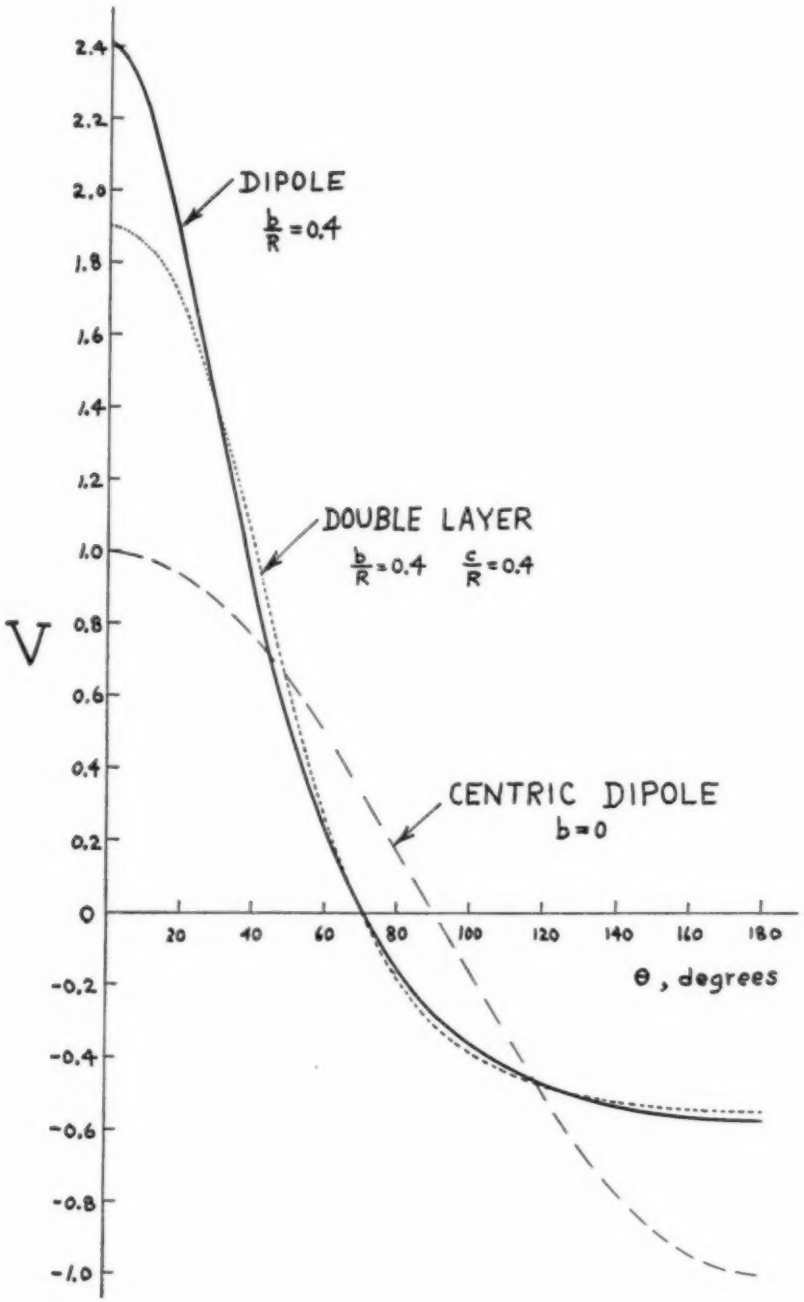

Fig. 4.—The dipole and double-layer potentials as a function of position on the sphere of Fig. 3 for a double-layer radius equal to 40 per cent of the sphere radius R and for eccentricity equal to 40 per cent of the sphere radius. The largest discrepancies are seen to occur near $\theta = 0$ but the potentials are nearly coincident over most of the spherical boundary. The centric dipole boundary potential is indicated by the dashed curve and departs much more from the eccentric dipole potential than does the eccentric double layer potential. All potentials have been normalized using $3p/4\pi\gamma R^2 = 1.0$.

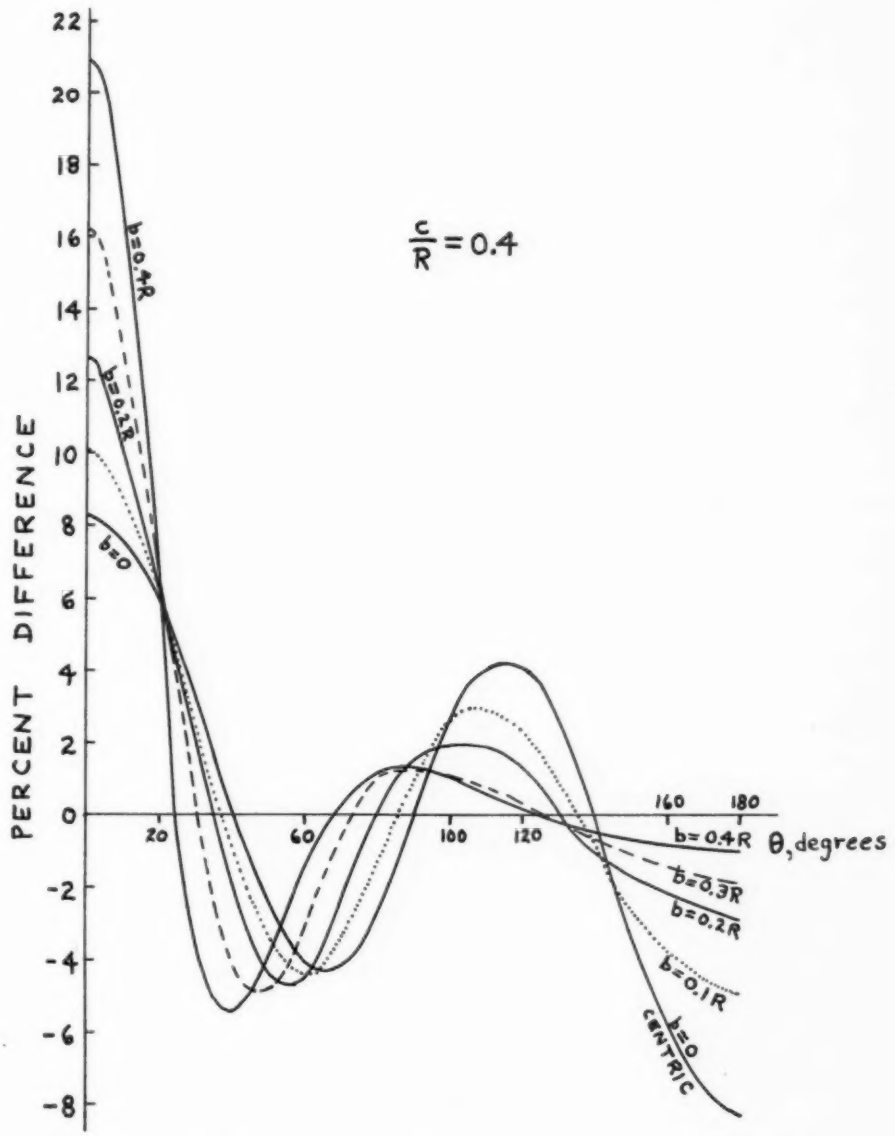

Fig. 5.—The per cent difference between dipole and double-layer potentials, defined in Equation (4), as a function of position on the sphere for a double-layer radius equal to 40 per cent of the sphere radius R and for eccentricities ranging from zero to 40 per cent of the sphere radius. A similar trend of results is obtained for smaller double-layer radii. The per cent difference can be seen to be very small except in a ± 18° cone centered on the double-layer axis.

The results given in Fig. 6 show the manner in which the maximum per cent difference, which occurs at $\Theta = 0$, depends upon the double-layer radius and eccentricity. However, if Θ is in the range 18° to 180°, the actual per cent difference is equal to or less than that given by the centric curve in Fig. 6 for all values of b between 0 and 0.4R.

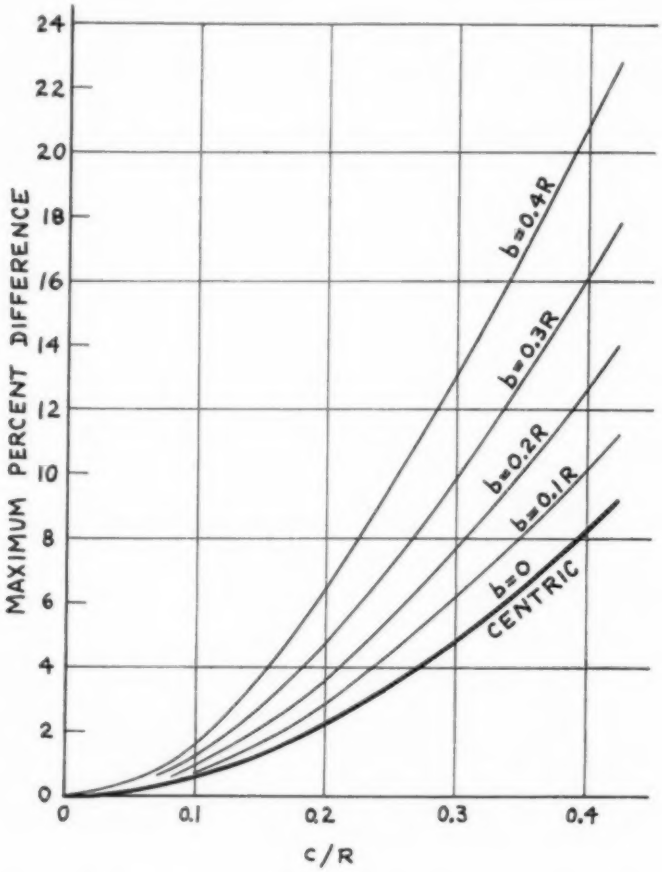

Fig. 6.—The maximum per cent difference between the double-layer and "equivalent" dipole potentials as a function of double-layer radius c with eccentricity b as a parameter. These maximum differences occur at $\Theta = 0$ (see Figs. 4 and 5). For Θ outside the range 18°, the actual per cent differences are equal to or less than that given by the centric curve for all values of b between 0 and 0.4R.

DISCUSSION

The ranges of values of double-layer radius c and eccentricity b were chosen to represent presently-accepted estimates of the volume occupied by the human ventricles within the chest, based upon posteroanterior roentgenograms of human subjects. A typical ratio of ventricle diameter to chest diameter is roughly 0.3 and typical ventricle eccentricities from the center of the torso are about 0.3 times the chest radius. Thus, values of c = 0.4R and b = 0.4R are probably

larger than would be encountered in most individuals; 0.3R is considered to be a more representative maximum value for both c and b. Consequently, it can be seen from curve $b = 0.3R$ in Fig. 6 with $c/R = 0.3$ that the maximum per cent difference between the eccentric dipole and double-layer potential is approximately 10 per cent, and this is considered to be a representative maximum figure for the frontal plane of the human subject.

The probability of encountering the maximum per cent difference is rather small owing to the very pronounced peak as a function of θ (see Fig. 5). In terms of the frontal-plane vectorcardiogram, consider the direction of the maximum value of the heart vector. If there are no electrodes on the body of the subject within $\pm 18°$ of this direction, the significant deviations between the eccentric dipole and double-layer potentials at the electrode positions actually used would be only about 5 per cent or less, as can be seen from the centric curve in Fig. 6.

A qualitative explanation of these very small discrepancies can be found in considering pairs of dipoles which constitute the double layer. Since the potential produced at a given point by the double layer is proportional to the solid angle subtended at that point, a circular double-layer disc is equivalent to the actual dome-shaped double layer. Now consider, for example, one elementary dipole at the rim of the double-layer disc. The potential produced at the surface of the sphere by this dipole departs markedly from that which would be produced by the same dipole at the center of the disc (assuming the disc radius is an appreciable fraction of the medium dimensions). However, if a second elementary dipole of the double layer located diametrically opposite the first and equidistant from the disc center is considered in combination with the first, a compensating effect is introduced such that the potential produced by this pair of dipoles, a distance 2c apart, is very nearly the same as that which would be produced if the pair of dipoles were located at the center of the disc. In view of this compensating effect, all of the elementary dipoles of the double layer can be considered in diametrically opposite pairs, leading to the qualitative conclusion that a single dipole at the center of the disc with the same total moment as that of the double layer will produce approximately the same potential as the double-layer disc. As the disc radius and eccentricity become larger, the compensating effect is less complete so that the difference between dipole and double-layer potentials increases.

The major importance of this analysis is the conclusion that the eccentric dipole approximation is excellent despite the fact that the distance from a point on the body (where an electrode is placed) to the heart is not large in comparison with the electrically active portions of the heart. Of course, this conclusion must be tempered by the assumptions which underlie the analysis. In particular, the application to chest electrodes, which do not lie in the frontal plane, should be clarified. It might appear from this analysis that the eccentric dipole approximation is sufficiently accurate to render inconsequential the difference in information obtained regarding ventricular depolarization from chest electrodes as compared with more distant electrodes. However, the distance from the human ventricles to chest electrodes is smaller than to limb electrodes. Also, the analogy

between a spherical boundary and the human torso may become more tenuous in the case of chest electrodes as compared with limb electrodes. Therefore, the results of this analysis may not be as applicable to chest electrodes as they are to limb electrodes. But it should be noted that the location of the "equivalent" dipole is at the center of the rim of the double layer; hence, even when portions of the ventricle double layer are very close to the surface of the chest, the "equivalent" dipole generally lies further inside the body and could well lie within the range of eccentricities considered here.

It is tempting to extend the results of this analysis to other boundary shapes which approach more closely that of the human torso. It is probably safe to say that the results of this analysis would not depart drastically from those which would pertain to a more complicated boundary geometry. Order-of-magnitude changes in the per cent difference between the eccentric dipole and double-layer potentials would certainly not be expected, although details of the behavior might differ somewhat from the typical curves given in Fig. 5. However, the effects of inhomogeneities, which have not been considered here, may have a very decided effect on the results. For instance, if a very favorable conduction path existed between certain portions of the double layer and the medium boundary, rather large departures between the double layer and the "equivalent" dipole might be encountered. Since the degree of inhomogeneity of the human subject has not been established accurately,[10] nor the effects of inhomogeneities on the boundary potentials, any analysis based upon the assumption of homogeneity should be subject to reservations.

In this analysis, the eccentric double layer was compared with a dipole having the same eccentricity, and the calculated differences in potential were seen to be very small. It is here emphasized that the dipole approximation is good only if the dipole is eccentric by the same amount as the double layer which it replaces. The effects of eccentricity are very significant, as discussed in detail elsewhere,[11] and the difference in potentials produced by an eccentric double layer and a centric dipole can become extremely large. This can be seen readily from the following example: the ratio of the maximum boundary potential produced by a dipole with eccentricity $b = 0.4R$ (whose axis passes through the sphere origin) to the maximum potential produced by an eccentric dipole of the same moment is 2.4:1 (see Fig. 4). Indeed, the eccentricity effects are much more pronounced than the differences between dipole and double layer; thus, the relatively unexplored effects of variable eccentricity during the heart beat would appear to be of great importance.

In conclusion, it must be restated that the results of this analysis should be interpreted carefully in light of the assumptions upon which they rest. Strictly speaking, it has been shown that the boundary potential produced by a uniform, eccentric, circular-rim double layer in a homogeneous conducting sphere is substantially the same as that of an equally eccentric dipole of the same total moment and orientation. While it is attractive from the standpoint of simplicity to conclude that an eccentric current dipole is an accurate representation of the electric current generated by the human heart, the enormous complexity of the heart

generator and the torso medium should be borne in mind constantly. Quantitative conclusions which rest upon idealized and simplified models should be subject to review frequently, and it is likely that such conclusions might require modification with the forthcoming of additional experimental evidence and more refined theoretical treatment.

It is a pleasure to acknowledge the accurate work of Mrs. F. Y. Niu in carrying out the computations based on Equation (3). The author is also greatly indebted to Dr. C. F. Kay and Dr. H. Schwan for many extremely helpful comments and criticisms, and to Dr. S. R. Warren, Jr., for the guidance offered in the pursuit of this investigation.

APPENDIX I

A double-layer current source of uniform moment M per unit area with a circular rim of radius c whose center is a distance b from the sphere origin O, shown in Fig. 3, and whose axis passes through the sphere center, produces a potential in the homogeneous, spherical conducting medium that must satisfy Laplace's equation

$$\nabla^2 V = 0 = \frac{\partial}{\partial r}\left(r^2 \frac{\partial V}{\partial r}\right) + \frac{1}{\sin\theta}\frac{\partial}{\partial \theta}\left(\sin\theta \frac{\partial V}{\partial \theta}\right) + \frac{1}{\sin^2\theta}\frac{\partial^2 V}{\partial \phi^2} \tag{5}$$

where r,θ and ϕ are spherical polar coordinates. In addition, the potential V must satisfy the following conditions:

(a) $\partial V/\partial \phi = 0$, since z-axis symmetry exists.

(b) V must reduce to the potential produced by the double layer in a medium of infinite extent when the sphere radius R is allowed to approach infinity.

(c) $\partial V/\partial r = 0$ at $r = R$, since the radial (normal) component of the current density must be zero at the perfectly insulating boundary.

If V is a convergent series containing a typical term of the form

$$(A_n r^n + B_n r^{-n-1})\, P_n(\cos\theta) \tag{6}$$

it will satisfy Equation (5) and the symmetry condition (a). A_n and B_n are constants, n is any positive integer and P_n is the Legendre polynomial of degree n.[12]

Condition (b) reveals a great deal about the nature of the solution, so the potential produced by the double layer in an infinite medium will be investigated. Since the potential produced by a uniform double layer at any field point $P(r,\theta,\phi)$ is proportional to the total solid angle subtended by it at P, any convenient double layer of the same moment M per unit area whose rim coincides with the circle of radius c can be selected for the purposes of analysis. A double layer on the surface of a sphere of radius h and center at 0 is a useful choice; one ring of this double layer is shown in Fig. 7. After obtaining the contribution to the potential of this ring, it is possible to integrate over all such rings between $a = \cos^{-1}(b/h)$ and $a = 0$ to obtain the total potential at P due to the double layer residing on the spherical surface of radius h, which is the same as that of the original double layer.

To obtain the potential due to the ring double layer, first consider the potential produced by an infinitesimal current in the shaded area da of the ring shown in Fig. 7. The potential produced at P by this current element is given by the elementary relation

$$dV_1 = \frac{J\, da}{4\pi\gamma s} \tag{7}$$

where J is the surface current density of the shaded element of area da, and γ is the conductivity of the medium. The distance between da and P is s and may be expressed as[12]

$$\frac{1}{s} = (r^2 + h^2 - 2rh\cos\beta)^{-\frac{1}{2}} = \frac{1}{r}\sum_{n=0}^{\infty}\left(\frac{h}{r}\right)^n P_n(\cos\beta), \quad r>h \tag{8}$$

and from Fig. 7

$$\cos\beta = \sin a \sin\Theta\cos(\phi_1 - \phi) + \cos a\cos\Theta. \tag{9}$$

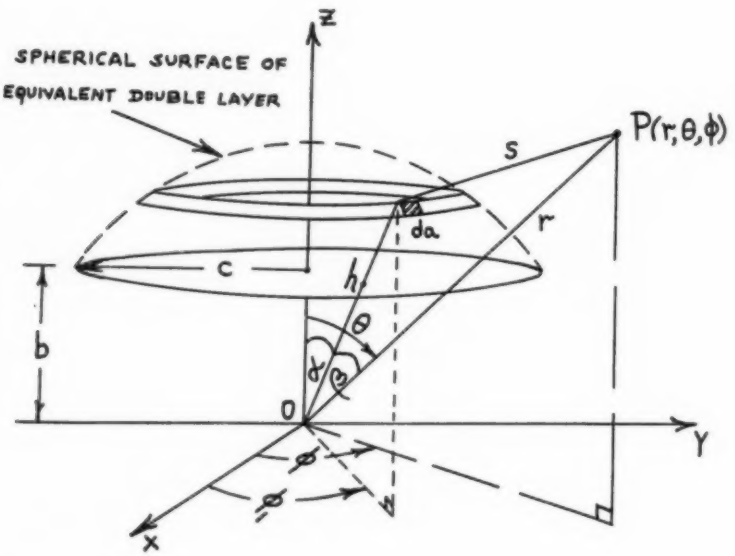

Fig. 7—Diagram illustrating the parameters used in integrating over the double-layer surface See also Fig. 3.

Now a double layer element of area da which resides on the surface of the sphere of radius h gives rise to a potential which is proportional to the derivative of dV_1 with respect to h; that is,

$$dV_\infty = \frac{M\ da}{4\pi\gamma}\frac{1}{r}\sum_{n=1}^{\infty}\frac{n\,h^{n-1}}{r^n}P_n(\cos\beta), \quad r>h \tag{10}$$

where dV_∞ is the contribution to the potential at P of the double-layer current element of area da and moment M per unit area on the ring of Fig. 7. Although $da = h^2\sin a\ d\phi_1\ d\ a$ and is a function of h, da must be held constant in order to obtain the correct double-layer expression by this derivative technique.

To obtain the total potential at P owing to the entire double layer, integrate Equation (10) with respect to ϕ_1 and a, holding r,Θ and ϕ constant.

$$V_\infty = \int_{a=0}^{\cos^{-1}(b/h)}\int_{\phi_1=0}^{2\pi} dV_\infty. \tag{11}$$

The most convenient way in which to perform the integration with respect to ϕ_1, which yields the potential produced by one ring, is to let the ϕ-coordinate of P be $\phi = 0$ for convenience. Then the following relation[12] can be used for $P_n(\cos \beta)$:

$$P_n(\cos \beta) = \sum_{m=0}^{m=n} (2 - \delta_m^o) \frac{(n-m)!}{(n+m)!} P_n^m(\cos a) P_n^m(\cos \Theta) \cos m \phi_1 \tag{12}$$

where P_n^m are associated Legendre functions of the first kind and δ_m^o is the Kroneker delta; $\delta_m^o = 1$ if $m = 0$ and $\delta_m^o = 0$ if $m \neq 0$. Since the integral from 0 to 2π of $\cos m\phi_1$ is zero except for $m = 0$, in which case the integral is 2π, it follows from Equations (10), (11) and (12) that

$$V_\infty = \int_{a=0}^{\cos^{-1}(b/h)} \frac{M}{4\pi\gamma} h^2 \sin a \, da \, \frac{1}{r} \sum_{n=1}^{\infty} \frac{n h^{n-1}}{r^n} 2\pi P_n(\cos a) P_n(\cos \Theta), \quad r>h \tag{13}$$

which may be written

$$V_\infty = -\frac{M}{2\gamma} \sum_{n=1}^{\infty} n\left(\frac{h}{r}\right)^{n+1} P_n(\cos \Theta) \int_{a=0}^{\cos^{-1}(b/h)} P_n(\cos a) \, d(\cos a), \quad r>h \tag{14}$$

and then integrated to obtain

$$V_\infty = \frac{M}{2\gamma} \sum_{n=1}^{\infty} n\left(\frac{h}{r}\right)^{n+1} P_n(\cos \Theta) \left[\frac{P_{n-1}\left(\frac{b}{h}\right) - P_{n+1}\left(\frac{b}{h}\right)}{2n+1}\right], \quad r>h. \tag{15}$$

However, by using the identity

$$P_{n-1}\left(\frac{b}{h}\right) - P_{n+1}\left(\frac{b}{h}\right) = \frac{2n+1}{n(n+1)} \left(\frac{c}{h}\right)^2 P_n'\left(\frac{b}{h}\right) \tag{16}$$

Equation (15) may be written more compactly as

$$V_\infty = \frac{Mc^2}{2\gamma} \sum_{n=1}^{\infty} \frac{1}{n+1} \frac{h^{n-1}}{r^{n+1}} P_n(\cos \Theta) P_n'\left(\frac{b}{h}\right), \quad r>h \tag{17}$$

where P_n' is the first derivative of P_n with respect to its argument, b/h. This is the desired result for the potential produced by the equivalent double layer in an infinite medium, to which the potential must reduce if $R \to \infty$.

The expression for V_∞ in Equation (17) suggests a solution containing terms of the type given in Equation (6) of the form

$$V_P = \sum_{n=1}^{\infty} (A_n r^n + B_n r^{-n-1}) P_n(\cos \Theta). \tag{18}$$

If this is to be a solution it must satisfy the boundary condition (c); hence,

$$\left.\frac{\partial V_P}{\partial r}\right]_{r=R} = 0 = \sum_{n=1}^{\infty} [nA_n R^{n-1} - (n+1) B_n R^{-n-2}] P_n(\cos \Theta) \tag{19}$$

and since Equation (19) must hold for all Θ, then A_n and B_n must be related by

$$A_n = \frac{n+1}{n} \frac{B_n}{R^{2n+1}}. \tag{20}$$

Inserting this into Equation (18) yields

$$V_P = \sum_{n=1}^{\infty} B_n \left(\frac{n+1}{n} \frac{r^n}{R^{2n+1}} + \frac{1}{r^{n+1}} \right) P_n(\cos \Theta) \tag{21}$$

and the B_n can now be determined from Equation (17) by allowing R to approach infinity in Equation (21), whence,

$$B_n = \frac{Mc^2}{2\gamma} \frac{h^{n-1}}{n+1} P_n'\left(\frac{b}{h}\right). \tag{22}$$

So, the final solution for V_P at any point in the spherical medium for which $r>h$ becomes

$$V_P = \frac{Mc^2}{2\gamma} \sum_{n=1}^{\infty} \left(\frac{n+1}{n} \frac{r^n}{R^{2n+1}} + \frac{1}{r^{n+1}} \right) \frac{h^{n-1}}{n+1} P_n'\left(\frac{b}{h}\right) P_n(\cos \Theta), \quad r>h. \tag{23}$$

The potential at the surface of the sphere is obtained by setting $r = R$ in Equation (23) which results in

$$V = \frac{Mc^2}{2\gamma R^2} \sum_{n=1}^{\infty} \frac{2n+1}{n(n+1)} \left(\frac{h}{R}\right)^{n-1} P_n'\left(\frac{b}{h}\right) P_n(\cos \Theta). \tag{24}$$

Finally, using $p = \pi Mc^2$ for the double-layer total moment, this may be written in the form given in Equation (1).

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STUDIES ON THE MECHANISM OF VENTRICULAR ACTIVITY. V.

Intramural Depolarization Potentials in the Normal Heart With A Consideration of Currents of Injury in Coronary Artery Disease

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CURRENT concepts of the nature and manner of propagation of the excitation wave in mammalian ventricles stem from the pioneer work of Thomas Lewis and Rothschild,[1,2] whose original observations were largely corroborated and later extended by Wilson and co-workers.[3-5] Lewis and Rothschild traced the course of the excitation wave on the surface of the dog's ventricles during normal sinus rhythm by comparing the intrinsic deflections in multiple epicardial leads. A similar technique was applied later to determine the order of ventricular depolarization during experimentally produced bundle branch block.[6,7] From these fundamental studies, a theory has been developed which is generally believed to explain specific cardiographic patterns in terms of electrophysiologic changes within the ventricular myocardium. With few exceptions,[8-10] however, direct observation of electrical activity in the ventricles has been limited to explorations of the epicardial surface and cavities. The present paper reports an investigation of intraventricular potentials during normal sinus rhythm registered by means of a specially designed electrode located at various depths within the ventricular wall, the interventricular septum, and the papillary muscle of the dog. It is suggested that evidence obtained in these and subsequent intramural studies may necessitate a modification of basic theories concerning the manner of cardiac excitation and the genesis of clinical electrocardiograms.

MATERIALS AND METHODS

Electrodes.—In order to record potentials within the ventricular myocardium, an ideal electrode must fulfill certain specifications, including (a) sufficient rigidity to withstand passage into and through the ventricular wall, (b) nonpolarizability, and (c) a recording surface small enough to register local potentials and minimize myocardial injury incident to insertion of the electrode.

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These requirements were largely met by the specially designed "plunge" electrode used in the present study. A fine (0.020 gauge) tempered silver wire 3 to 4 cm. in length was insulated throughout with polysterene cement and enamel except for a segment of about 0.5 mm. at the extreme tip which formed the recording surface; the latter was filed to a sharp point and chlorided by immersion in dilute hydrochloric acid through which an electric current was passed. Markings placed at 5 mm. intervals along the wire indicated the depth of the recording tip when the electrode was plunged into the ventricular wall. In order to compare the results obtained with different materials, platinum or tungsten was substituted for silver in several electrodes. Intramural tracings recorded with the platinum or tungsten electrodes were essentially similar to those obtained with silver electrodes, indicating that either material was suitable for purposes of the study. Recently, Scher and associates[10] have successfully recorded intramural potentials with a tungsten electrode considerably smaller in diameter than the one here described.

Potentials within the interventricular septum were recorded with a curved wire made of the same tempered silver and insulated in the same manner as the intramural electrode. A chloride-coated segment, 0.5 mm. in length, at the mid-point of the wire formed the recording surface. The curved electrode was passed through the wall of one ventricle and its cavity, the interventricular septum, and finally the cavity and wall of the opposite ventricle, tracings being recorded in succession from several septal sites.

Records from the epicardial surface of the heart were obtained with a small pledget of cotton, approximately 2 mm. square, soaked in normal saline solution. Attached to the cotton pledget was a fine silver wire, which in turn was spliced to an insulated copper wire. The surface electrode could be applied manually to any point on the cardiac surface by holding the insulated wire and could be secured in any desired location with a suture.

Electrocardiograph.—The majority of leads were registered on a dual-channel Brush recorder operated at the maximum paper speed of 125 mm. per second, five times the usual rate. Deflections thus obtained are so spread out that each component can be studied in great detail with regard to timing, magnitude, and configuration. In all experiments the indifferent electrode was connected to Wilson's central terminal. Tracings were recorded at an attenuation of 20x, with the standardization adjusted so that a potential of 20 mv. caused a 15 mm. deflection. The amplifying system of a Sanborn Polyviso was used to activate the Brush recorder, both channels of the recorder being standardized at the beginning and end of each series of observations. When run at its maximum paper speed, the Brush apparatus was found accurate to within 0.004 second. Frequency response curves determined for this instrument did not drop off appreciably until 30 cycles per second.

For purposes of comparison, a series of experiments was recorded on the photographic-writing Sanborn Twinbeam and direct-writing Sanborn Polyviso electrocardiographs as well as on the Brush recorder. The photographic-writing Sanborn shows no decay in frequency response until 400 or 500 cycles per second, while the direct-writing Sanborn is accurate at rates up to 50 cycles per second. Despite the difference in frequency response, all three machines yielded essentially similar deflections.

Procedure.—A total of thirty-two dogs was used in the study. All animals were placed in a supine position and anesthetized with morphine and urethane. Control limb and multiple precordial tracings were then made, after which the chest was opened, the lungs inflated, and artificial respiration instituted with an electric pump-respirator. Adequate exposure of the heart was achieved by removing two ribs on each side together with the sternum.[11a] Small windows, roughly 1 cm. in diameter, cut in the pericardium over the ventricle proved most practical; plunge electrodes inserted through these windows underwent relatively little motion, whereas excision of the entire pericardium would permit such extravagant cardiac movements that the electrodes could not be retained in position. A constant intravenous infusion of 0.1 per cent procaine in normal saline was maintained to minimize cardiac irritability during manipulation of the heart.

In each animal, electrocardiographic study began with the insertion of a plunge electrode through the free wall of the ventricle into the cavity where it remained throughout the experiment.

This lead was recorded simultaneously with each epicardial or intramural lead; the onset of the downstroke in the cavity tracing served as a reference point for timing the onset of the surface and intramural QRS deflections. Surface leads from various regions of both ventricles were taken through the pericardial windows, after which plunge electrodes were thrust into the ventricular wall at the same sites. Effort was made to insert the plunge electrode at right angles to the epicardium. During its transmural passage, the plunge electrode was halted at 3 to 5 mm. intervals, as intramural tracings from each level were recorded periodically for several minutes until currents of injury became minimal. Finally, when the plunge electrode penetrated the endocardium, the cavity potential was recorded. Since the left ventricular wall of the beating heart in most animals was 15 to 20 mm. in thickness, from 3 to 5 intramural tracings were obtained from each electrode. Fewer levels were explored in the thinner wall of the right ventricle. After the electrocardiographic studies had been completed, the heart was removed and gross sections of the ventricle were made with the plunge electrodes in situ. In only two instances was the plunge electrode found to have entered the wall so obliquely that the depth of the recording tip was significantly different from that indicated by the markings on the wire.

Recording Properties of the Plunge Electrode.—By recording leads at various measured depths throughout both ventricles, as described, an approximate concept of the distribution of intramural potentials during normal ventricular depolarization has been obtained. The accuracy of this concept, however, depends upon two assumptions: (1) That the normal depolarization process was not altered by the presence of the plunge electrode, and (2) that the electrode registered essentially local potentials in the immediate vicinity of its recording surface. These technical factors must be considered before the results of the study are evaluated.

(1) The objection has been advanced that a recording electrode in the ventricular wall may induce focal block or other artifacts which alter the normal depolarization process and therefore may yield abnormal QRS complexes. In all experiments performed on the normal heart, the intramural QRS deflections registered by plunge electrodes were equal in width to the QRS waves in surface and cavity leads, establishing that the duration of depolarization was not detectably altered by the intramural electrode. In order to determine if the shape as well as the width of the depolarization complex was unaffected by the plunge electrode, a simple experiment was performed. In each of six animals, a cotton electrode was fixed to the epicardium of the ventricle and a plunge electrode inserted obliquely into the ventricular wall almost parallel to the surface so that its recording tip lay in the myocardium as close as possible beneath the cotton electrode. If perifocal block or any other local abnormality of depolarization were induced by the plunge electrode, an abnormal QRS complex should appear in the subepicardial lead but not in the simultaneously recorded epicardial lead. Actually, the QRS complexes in the two leads closely resembled one another in shape (Fig. 1, *A*). The T waves of the subepicardial and surface leads also were similar, but current of injury consistently appeared more prominent in the former.

The absence of electrode-induced artifacts in the intramural tracings was further shown by the consistent finding that subendocardial leads, registered within a few millimeters of the endocardium, exhibited QRS complexes similar to those in cavity leads from subjacent sites. As the plunge electrode was passed from subendocardial muscle into the cavity, the shape of the QRS and T waves remained almost constant (Fig. 1, *B*). If abnormalities of depolarization were induced and recorded by the subendocardial electrode, these abnormalities would have disappeared from the tracings when the cavity was entered. Thus, it was demonstrated that the intramural QRS complexes characteristically obtained during the study were not significantly influenced in width or shape by electrode-induced disturbances. Although perifocal block or other disturbances of depolarization occurred on rare occasions, they were recognized without difficulty. These disturbances disappeared spontaneously after a short interval or after the electrode was reinserted.

Any direct insult to the myocardium may be expected to give rise to currents of injury which are manifested electrocardiographically as deviations of the S-T segment from the base line. Thus, even though the plunge electrode used in the present experiments was small, its insertion into the myocardium always elicited local injury currents. Since pronounced deviations of the

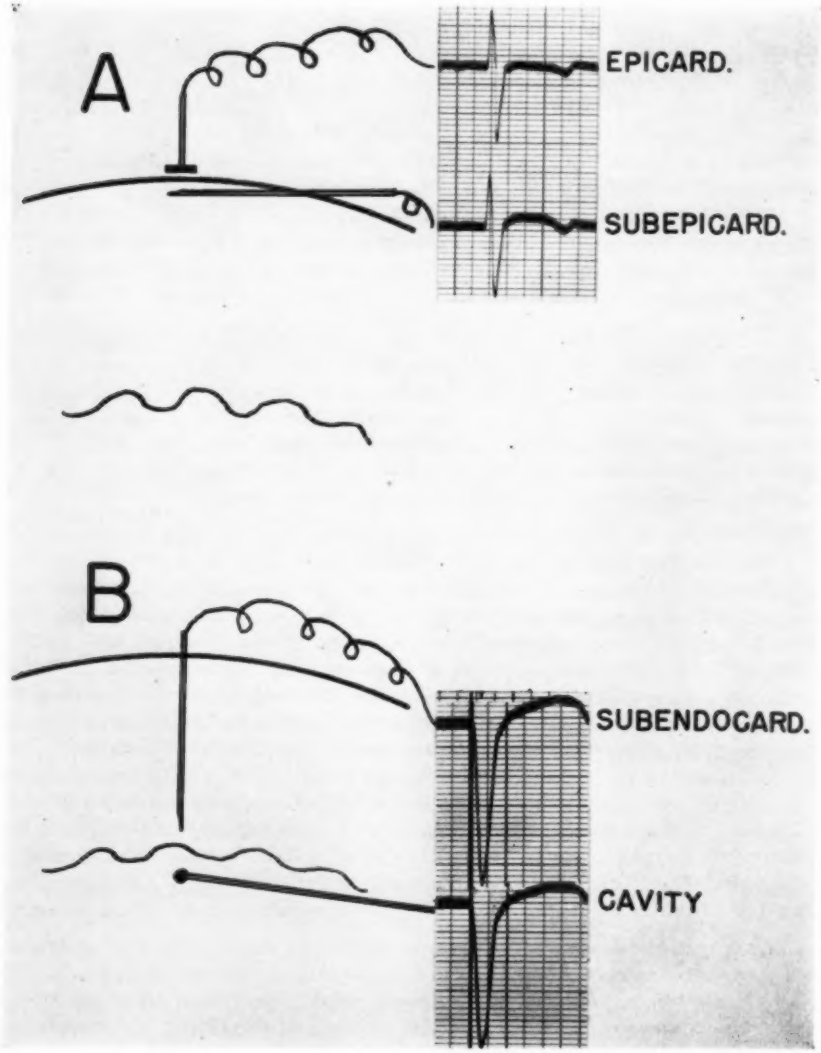

Fig. 1.—*A*, Epicardial lead from cotton electrode and simultaneously recorded subepicardial lead from plunge electrode located directly beneath cotton electrode. Both leads registered on Sanborn Photographic Twinbeam at paper speed of 75 mm. per second. QRS complexes in the two leads are equal in width and approximately similar in configuration, indicating that no focal block or other depolarization abnormality occurred in the vicinity of the plunge electrode.

B, Subendocardial and cavity leads recorded successively from plunge electrode in left ventricle. The subendocardial tracing was registered after injury current subsided, then the electrode was pushed through endocardium and the cavity tracing made. QRS complexes in the two records are identical, establishing that the intramural complex was not affected by electrode-induced abnormalities.

S-T segment distort the configuration of the preceding QRS complex, it was necessary to wait until the injury current subsided in order to record accurately ventricular depolarization potentials. This was done in all instances by making electrocardiograms at intervals of one minute after the plunge electrode reached each intramural level studied. The S-T segment, at first markedly elevated, exhibited a gradual return toward the base line as the S wave deepened and the R wave became smaller; finally, about 5 minutes after the electrode was inserted, lowering of the S-T segment usually stopped and the shape of the complex remained constant. Minimal elevation of the S-T segment generally persisted throughout the experiment. In a few tracings, however, the base line became essentially isoelectric several minutes after insertion of the electrode, indicating that injury currents had ceased.

According to certain workers, S-T segment deviation is caused by blocking of the depolarization process at the boundary of injury and, therefore, is always associated with a distorted QRS complex. Under such circumstances, the persistence of discernible injury currents throughout most of the present experiments might be presumed to have altered or obscured certain features of the normal depolarization wave. This possibility was investigated by comparing intramural leads exhibiting minimal S-T elevation with tracings from comparable levels in which the S-T segment eventually returned to the isoelectric line. In every instance the QRS complexes preceding the isoelectric interval were essentially similar to the complexes followed by minimal S-T deviation, indicating that the intramural depolarization potentials were not perceptibly affected by residual injury currents after the initial effect of electrode trauma had subsided.

(2) It is believed by some investigators that direct electrodes are influenced significantly by potentials of muscle cells remote from the recording surface.[14] The following theoretic and experimental observations indicate that this objection does not apply to the plunge electrodes used in the present study.

According to Poisson's Integral, the "potential of a given dipole as determined at a certain point within its electromotive field will vary in inverse relationship to the second power (for a volume conductor of infinite size) or to the third power (for a volume conductor of finite size) of the distance of this point from the center of the dipole."[5,15] The plunge electrode employed in the present experiments has an extremely small recording tip which is placed in intimate contact with the intramural myocardium. Theoretically, therefore, it should record mainly from a localized area immediately surrounding the recording tip and should be relatively uninfluenced by potentials in more distant areas.

In order to confirm that this theory applied to the plunge electrode, four experiments were devised:

(A) The effect of distant potentials upon the plunge electrode was investigated by comparing the auricular complexes in tracings recorded from the auricle, from the auriculoventricular groove, and from various points on the ventricle progressively more distant from the auricle. A rapid decline in the amplitude of the auricular P waves occurred as the electrode was moved away from the auricle over the surface of the ventricle. The auricular deflection was extremely small in epicardial tracings from plunge electrodes located as little as 2 to 3 mm. from the auriculoventricular groove and was invisible or barely discernible in surface leads recorded at a distance of 1 or 2 cm. from the auricle. In the innumerable intramural leads recorded during the study, evidence of a P wave was rarely seen although the electrode frequently was located near the vigorously beating auricle.

(B) Intramural leads were recorded from both ventricles during instances of experimentally produced bundle branch block. Activation of the unblocked ventricle caused comparatively small (2 to 3 mv.) or no deflections in tracings from the blocked ventricle. Even in the absence of local electrical activity, therefore, the plunge electrode was affected only slightly by potentials of muscle distant from the recording tip.

(C) The effect of local trauma at various measured distances from a plunge electrode was demonstrated by insertion of a second electrode. When the first electrode penetrated the myocardium, it promptly registered pronounced S-T segment elevation which gradually diminished as the injury current subsided. The second plunge electrode was then inserted as little as 5 mm. distant from the first electrode. Although the second electrode registered marked S-T segment

elevation for several minutes, tracings from the first electrode were unaffected by the nearby injury. Application of mechanical pressure near a plunge electrode likewise failed to produce S-T segment deviation after injury currents caused by insertion of the electrode had subsided.

(D) In each of four dogs, one ventricle was completely excised while continuous electrocardiograms were recorded from a plunge electrode located in the opposite ventricular wall. The intact ventricle continued to beat for a brief period following the excision. If depolarization of the contralateral ventricle affected the plunge electrode, it presumably would contribute to the negativity of the intramural complex. In no instance, however, did the plunge electrode register increased positivity after the opposite ventricle was removed. Although this experiment was necessarily crude, examination of the continuous intramural tracings revealed no significant change associated with the excision. Hence the potentials of the contralateral ventricle prior to its removal must have had little or no effect on the plunge electrode.

Obviously, some distant potentials may be recorded by an electrode, particularly if these forces are of considerable voltage during a period when there is little activity locally as in experiment (B). Nevertheless, the results of the preceding experiments, together with theoretic considerations, indicate that the plunge electrodes used in the present study record, almost exclusively, local events and are not influenced to a significant extent by activity occurring in muscle not in direct contact with the recording tip. This conclusion is consistent with the observations of Kisch,[16] who demonstrated that essentially local potentials were recorded by electrodes placed directly on the dying chicken's heart.

In contrast to plunge electrodes, the familiar precordial electrodes employed in clinical practice register potentials of many portions of the heart remote from the chest. The greater recording range of the precordial lead may be attributed to the fact that clinical electrocardiograms, generally, are registered at a standardization of 1 mv. equal to 10 mm., or approximately 15 times the sensitivity of the apparatus used to obtain intramural leads. Moreover, the precordial electrode has a recording surface many times greater than that of the plunge electrode. Finally, the angle subtended by the precordial electrode includes a large portion of the ventricular surfaces. Epicardial electrodes such as those used in the present study record from considerably smaller areas than the precordial electrode, but register somewhat less localized potentials than the plunge electrode because of their larger recording surface and the presence of saline, acting as a conductor on the surface of the heart.

DEPOLARIZATION POTENTIALS OF THE NORMAL VENTRICLES

Depolarization potentials during normal sinus rhythm were studied in the left ventricles of fifteen dogs, in the right ventricles of eleven dogs, and in the interventricular septa of ten dogs.

Epicardial Surface.—The depolarization complexes obtained from the surface of both ventricles consisted of a positive component usually followed by a negative component. The relative magnitude of the R and S waves varied considerably in epicardial leads from different dogs and from different portions of the same ventricle; this was particularly true of the right ventricle. As reported by previous investigators[1,5] the left ventricular surface yielded predominantly positive deflections consisting, on the average, of an R wave approximately twice as great in amplitude as the S wave. The right ventricular surface exhibited a somewhat smaller R:S ratio, except near the pulmonary conus which sometimes presented a purely positive surface deflection. In many instances, however, a negative component, or S wave, was recorded from the pulmonary conus.*

*According to the classic electrocardiographic theory of Wilson, an S wave in epicardial leads is attributable to activation of distant ventricular muscle after the region directly beneath the electrode has depolarized. Both electrocardiographically[1] and cinematographically[17], the pulmonary conus has been found to undergo depolarization later than any other part of the ventricles. Thus, the frequent occurrence of a negative component following the R wave in leads from the pulmonary conus appears incompatible with Wilson's explanation of the genesis of epicardial S waves.

Intramural Levels.—On twenty-four occasions in fifteen dogs, a plunge electrode was introduced into the free wall of the left ventricle and tracings made at various depths. As shown in Table I and Fig. 2, a rapid decrease in the amplitude of the R wave and an increase in the amplitude of the S wave were observed as the recording electrode penetrated the myocardium. At a depth of 5 mm. beneath the epicardial surface (approximately one-third of the distance between epicardium and endocardium), the R wave was entirely absent in some instances and was much smaller than the S wave in most of the remaining animals. At 10 mm. beneath the epicardium, a purely negative depolarization complex was obtained in about one-half of the tracings. Subendocardial muscle 15 mm. from the surface yielded a pure QS wave in all but five instances; the positive component in these 5 records consisted of a so-called "embryonic" R wave or a notch visible on the downstroke of the QS deflection. Generally speaking, among the left ventricles studied, positive potentials were found to predominate only in a superficial layer constituting approximately 20 per cent of the intramural myocardium; the innermost 80 per cent of the wall presented, primarily or entirely, negative depolarization waves.

The right ventricle, like the left ventricle, exhibited decreasing positivity and increasing negativity at progressively greater depths of the wall (Fig. 3). However, the outer zone of positivity appeared to involve a greater proportion of the right ventricle than of the thicker left ventricle. At 2 to 3 mm. beneath the surface (approximately one-third of the depth of the wall), the negative phase of the depolarization complex in right ventricular leads appeared larger than the positive component. Potentials in the innermost subendocardial layers were almost entirely negative, as evidenced by QS waves.

The distribution of intramural potentials was further studied by inactivating the outermost one-fourth to one-third of the left ventricular wall. Portions of the epicardium and underlying subepicardial muscle were severely burned with a cautery or hot glass rod in twenty-three dogs, destroyed by application of nitric acid or formaldehyde in thirteen dogs, and actually excised in five dogs. Direct leads from the inactivated surface or exposed intramural muscle consistently exhibited markedly less positivity than control tracings from the intact epicardium. In some instances the normal RS deflection was replaced by a QS wave. Thus the observation was confirmed that positive depolarization potentials prevail only at the epicardial surface and in a relatively thin subepicardial layer of the normal ventricular wall. Details concerning these experiments and their clinical significance are discussed in a subsequent paper on the pathogenesis of coronary QS and QR waves.

Previous investigations have revealed that the T wave is abnormally negative in unipolar leads from dogs with open chests. Contrary to the belief of Wilson and associates,[4] other workers[22] contend that the depolarization as well as the repolarization complex may be altered by opening the chest wall. In order to determine if this factor could account for the predominant negativity observed in intramural leads, two experiments were performed. In two animals, a small incision was made in the left side of the chest and several plunge electrodes were inserted to various depths of the ventricular wall. Each electrode was sutured

TABLE I. STATISTICAL ANALYSIS OF DEPOLARIZATION COMPLEXES IN INTRAMURAL LEADS

DEPTH (MM.)	NO. OF DETERMINATIONS	AMPLITUDE OF R WAVE (MM.)			AMPLITUDE OF S WAVE (MM.)			TIMING OF INTRINSIC DEFLECTION (SEC. × 10^{-2})		
		RANGE	AVERAGE	STANDARD DEVIATION	RANGE	AVERAGE	STANDARD DEVIATION	RANGE	AVERAGE	STANDARD DEVIATION
Surface	21	3.5–21.5	12.6	±5.0	12–0	4.8	±4.4	2.0–0.8	1.34	±0.32
5	20	8.0– 0.0	2.3	±2.2	30–10	19.0	±5.0	0.8–0.0	0.46	±0.26
10	20	2.0– 0.0	0.7	±0.9	33–13	24.8	±5.1	0.4–0.0	0.2	±0.19
15	16	0.5– 0.0	0.0	±0.1	32–15	25.1	±5.2	0.4–0.0	0.036	±0.015
20	7	0.0– 0.0	0.0	±0.0	25–14	20.7	±4.7	0.0–0.0	0.0	±0.0
Cavity	21	0.0– 0.0	0.0	±0.0	29–16	21.5	±4.1	0.0–0.0	0.0	±0.0

As the electrode traverses the wall from surface to cavity, the R wave becomes smaller while the depth of the S wave increases and then diminishes. Currents of injury may reduce the maximum amplitude of S waves but theoretically do not affect portions of the complex preceding the intrinsic deflection.[4]

The intrinsic deflections occur almost simultaneously at the onset of the QRS complex in subendocardial and cavity leads but appear progressively later in subepicardial leads as the distance between the electrode and the surface decreases. Rates of depolarization were calculated by dividing the distance between two electrode positions into the difference in time of onset of the intrinsic deflections recorded from these positions. Since slight (less than 0.004 second) differences in timing of the intrinsic deflections may not be detectable, depolarization rates over several thousand millimeters per second are immeasurable.

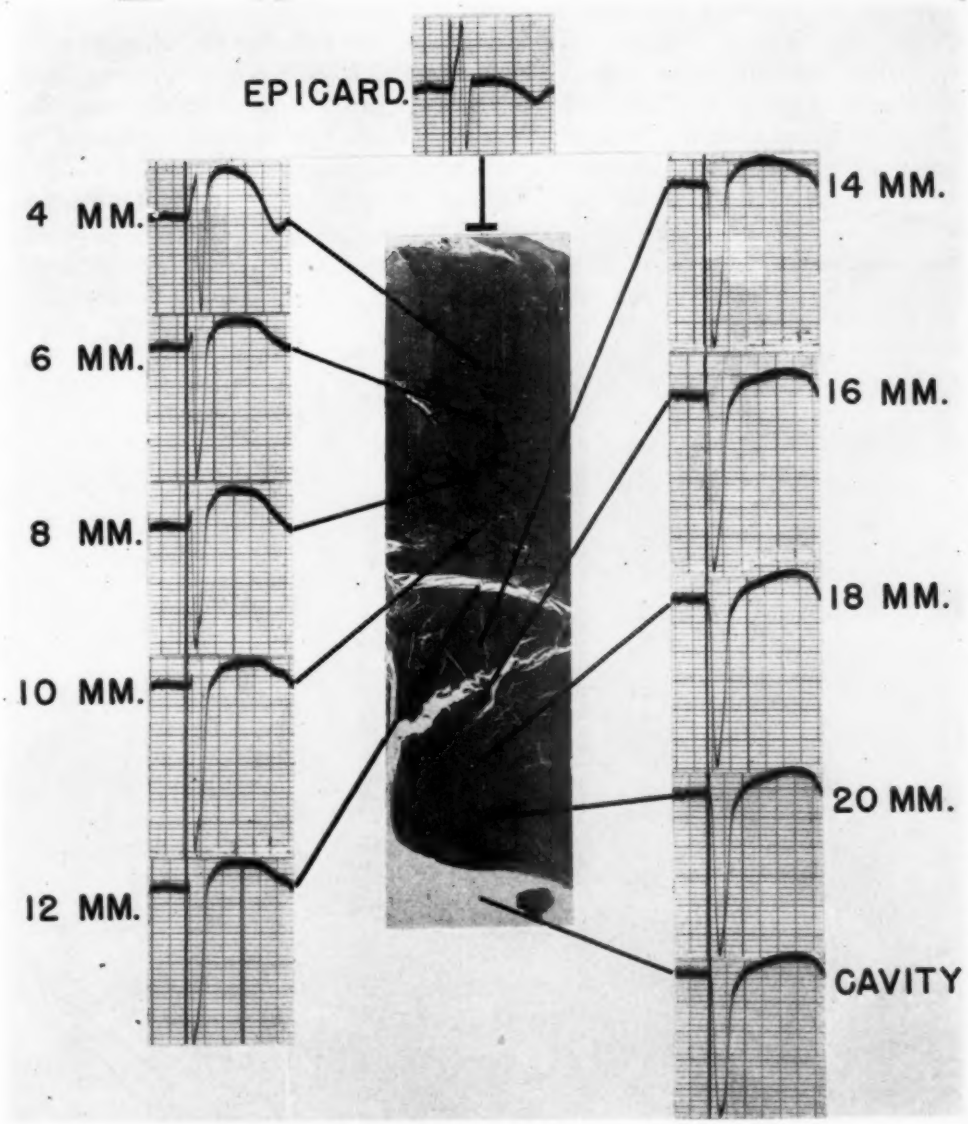

Fig. 2.—Epicardial, intramural, and cavity leads from left ventricle during normal sinus rhythm recorded on Sanborn Photographic Twinbeam at paper speed of 75 mm. per second. Black line in micro-photograph shows path of plunge electrode. Intramural tracings were recorded after injury currents reached a minimum.

The epicardial surface yields a diphasic depolarization complex. Tracing recorded 6 mm. beneath the surface exhibits a small positive component followed by a large negative deflection. At intramural depths of 14, 16, 18, and 20 mm., as well as in the cavity, a pure QS wave is obtained. Note that the intrinsic deflections at 14, 16, 18, and 20 mm. begin simultaneously, indicating that depolarization of the deeper layers of the wall occurs almost instantaneously. In contrast, the intrinsic deflections at 12, 10, 8, 6, and 4 mm. depths and at the surface occur progressively later, showing that the outer layers depolarize at a relatively slow rate.

in place, the lungs inflated, the incision closed, and intramural tracings recorded. Exposure of the heart was then achieved by opening the chest and removing several ribs together with the sternum as previously described, after which a second set of tracings was made. The intramural leads registered after closure of the small incision exhibited predominantly negative depolarization complexes similar to those obtained while the chest was open. In two other animals, an incision was made in the abdomen and several electrodes were plunged through the diaphragm and unopened chest wall into the ventricular myocardium where tracings were recorded at various depths. In this crude experiment, as in the first experiment, pure QS or rS waves almost consistently were obtained from intramural muscle within the closed chest cavity. The results of both experi-

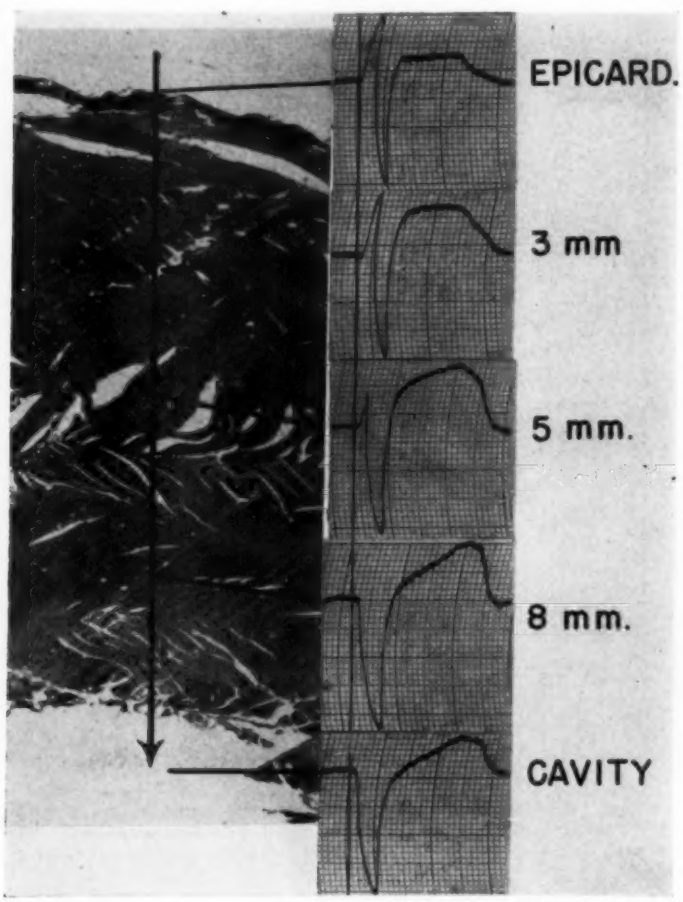

Fig. 3.—Epicardial, intramural, and cavity leads from the right ventricle during normal sinus rhythm recorded on the Brush recorder at 125 mm. per second paper speed. As in the left ventricle, the positive component of the depolarization complex diminishes and the negative component increases as the electrode traverses the wall from epicardium to endocardium. Both the cavity and adjacent subendocardial muscle yield pure QS waves. Note that the initial positive potential in the right ventricle is less marked at the epicardial surface but extends to proportionately greater intramural depths than in the left ventricle.

ments thus indicated that predominantly negative depolarization complexes are registered in unipolar intramural leads whether the chest wall is open or closed.

Rate of Intramural Depolarization.—In twenty-one instances an attempt was made to measure the velocity of the depolarization wave by timing the onset of the downstrokes in leads from various depths within the ventricular wall. Considerable doubt exists at present concerning the common assumption that the onset of the downstroke is the intrinsic deflection, representing the arrival of the excitation wave directly beneath the recording electrode. If this arbitrary assumption is correct, depolarization apparently occurs much more rapidly in the deeper layers of the myocardium than in the epicardial region. A comparison of the onsets of the downstrokes indicates that the innermost two-thirds of the ventricular wall depolarized at a rate of at least several thousand millimeters per second, while the more superficial layers depolarized at the relatively slow speed of 200 to 800 mm. per second.

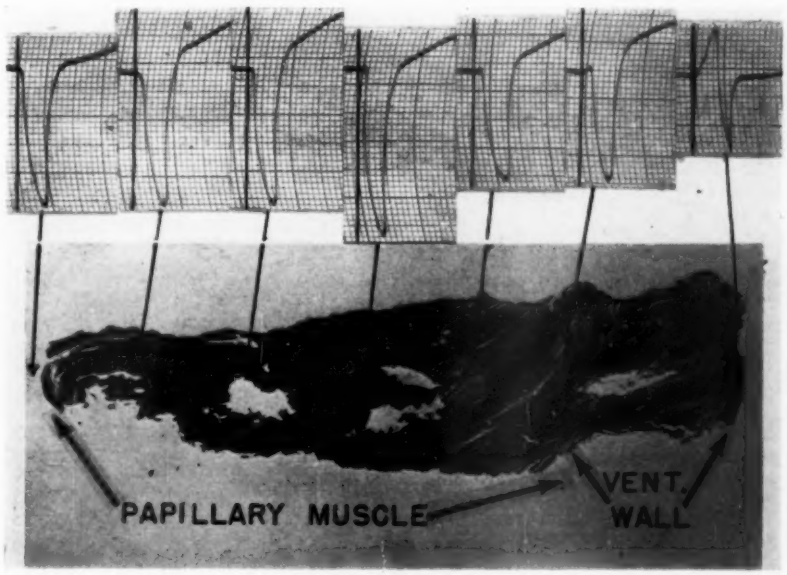

Fig. 4.—Microphotograph and electrocardiograms from a section of left ventricle including the papillary muscle. Recorded on the Brush recorder at 125 mm. per second. Epicardial surface (to the right) yields characteristic RS wave. A progressive decrease in the size of the positive component and an increase in the size of the negative component occurs as the plunge electrode is pushed deeper into the myocardium. All levels of the papillary muscle yield predominantly or entirely negative deflections.

Papillary Muscle.—In eight animals, tracings from a plunge electrode were made at multiple levels of the left papillary muscle, after which the electrode was sutured in place and its location verified post mortem. Because of technical difficulties, the right papillary muscle was not studied. The depolarization complexes obtained from all depths of the left papillary muscle were almost consistently negative (Fig. 4). Occasionally, an embryonic R wave was registered at variable points on the downstroke of the QS wave. The negative deflection recorded from the muscle consistently was greater in amplitude than the QS wave from the neighboring cavity.

Cavities.—Cavity leads were obtained in all animals by introducing a plunge electrode near the base of the heart and directing it downward toward the apex of the ventricles so that the left or right cavity was entered at an oblique angle nearly parallel to its long axis. The entrance of the electrode tip into the cavity was clearly manifested by a distinct sensation similar to that felt as a needle pierces the theca interna during lumbar puncture. Since the distance across the cavity from one endocardial surface to the other is extremely short, especially during systole, it was necessary to establish that the electrode had not penetrated the interventricular septum or papillary muscle. The most trustworthy evidence that the electrode tip remained within the cavity is an isoelectric S-T segment, indicating the absence of injury currents. In contrast to the plunge electrode, catheter electrodes used to record cavity tracings in patients often register currents of injury due to pressure of the electrode on endocardial surfaces surrounding the cavity. A second criterion which aids in distinguishing true cavity leads is the configuration of the negative wave; the downstroke of this deflection usually is less abrupt in cavity tracings than in records from the mural endocardium or septum.

In the left ventricle, pure QS waves were consistently recorded from all portions of the cavity tested. Both the configuration and the amplitude of the QS wave varied in tracings from different cavities and from different parts of the same cavity; the deflection was deepest in leads from the apex, less deep in leads from the base, and shallowest in leads from the septal region. As compared with the intramural QS waves recorded from adjacent subendocardial tissue, the cavity QS was identical in time of onset but significantly smaller (Fig. 2). The isoelectric S-T segment in left cavity leads was followed by an upright T wave somewhat lower in amplitude than the T waves recorded from intramural and epicardial regions.

In nine of the eleven right ventricles studied, leads from various portions of the cavity were similar to their counterparts from the left ventricle, displaying pure QS waves followed by isoelectric S-T segments and upright T waves (Fig. 3). In two instances, a tiny R wave measuring approximately 0.5 mm. in amplitude followed by a deep S wave was recorded from one portion of the right cavity; since these rS waves resembled the depolarization complexes characteristically recorded from the right septal surface, the cavity electrode presumably was near the septum.

Interventricular Septum.—When the curved electrode was passed through the septum from right to left as described previously, the following sequence of electrocardiographic patterns was recorded: As the right side of the septum was entered, a small R wave followed by a deep S wave appeared. The septal R wave grew progressively larger in amplitude until the electrode had advanced to a point approximately midway between the septal surfaces, after which it rapidly decreased in height. By the time the left surface of the septum had been reached, the R wave was replaced by a QS deflection. The entrance of the electrode into the left ventricular cavity was demonstrated by the sudden return of the S-T segment to the base line, indicating disappearance of injury currents (Fig. 5).

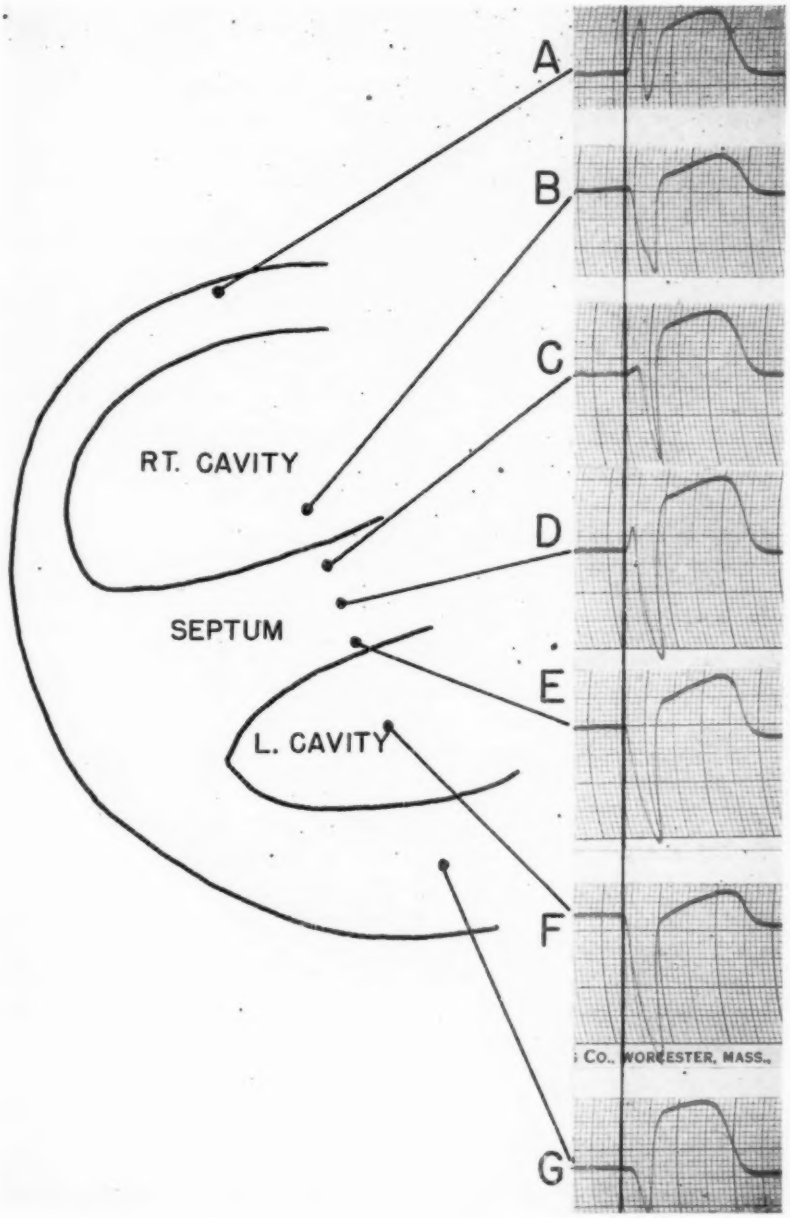

Fig. 5.—Series of electrocardiograms recorded by curved septal electrode traversing ventricles from right to left. Recorded on the Brush recorder at paper speed of 125 mm. per second. Diagram shows approximate size from which each record was made. *A*, Near the right ventricular surface, an rS wave is obtained. *B*, Cavity QS deflection. The right side of the septum yields a small initial R wave (*C*) which grows larger as the electrode approaches the center of the septum (*D*), then diminishes and finally disappears near the left septal surface (*E*). *F*, Characteristic QS deflection from left cavity. *G*, A QS wave considerably less deep than the cavity QS is obtained from the middle of the left ventricular wall.

INTENSITY OF SUBEPICARDIAL AND SUBENDOCARDIAL INJURY CURRENTS

During the course of the study, it was repeatedly noted that the S-T segment elevation recorded by plunge electrodes immediately after their insertion into the ventricular wall was much more marked in subepicardial leads than in tracings from greater intramural depths. This surprising observation has been confirmed by the following experiment: On ten occasions in six animals, a plunge electrode was inserted in the left or right ventricular wall near the surface and an electrocardiogram recorded before the injury current declined. The electrode was then pushed a few millimeters farther into the wall, where a second tracing was promptly made. This procedure was repeated, records being obtained at 2 to 5 mm. intervals, until the cavity was reached. Comparison of the successive tracings revealed that injury currents recorded near the surface consistently were more intense than those near the cavity. In most instances the RS-T segment showed a progressive but irregular decline as the electrode traversed the wall from epicardium to endocardium (Fig. 6).

Initially, the observed difference in intensity of the injury current at various intramural levels was attributed to differences in the mobility of the recording electrode. The tip of an electrode in subepicardial tissue exhibited greater magnitude of motion, and therefore was presumed to cause more intense local trauma, than an electrode tip buried in the deeper myocardial layers. The following experiment, performed in four animals, tested this hypothesis. One plunge electrode was inserted into the subendocardial tissue and another into the subepicardial zone; as expected, the S-T segment was more elevated in the subepicardial lead. The subendocardial electrode was then deliberately moved back and forth in order to simulate the movement of the subepicardial electrode caused by the motion of the heart. Despite repeated manipulation, the S-T segment in the subendocardial lead remained practically constant and significantly lower than in the subepicardial tracing. These results indicate that the greater intensity of the injury currents recorded from superficial intramural layers cannot be explained as an artifact arising from excessive motion of the subepicardial electrode. Rather, in response to direct trauma, subendocardial muscle apparently is prone to produce much weaker injury currents than more superficial layers of the ventricular wall.

DISCUSSION

Intramural Depolarization.—Current concepts of the mode of ventricular depolarization are derived from Bernstein's membrane theory as applied to cardiac muscle by Craib[18] and Wilson and associates.[5] According to these workers, the depolarization process may be considered as an advance of dipoles, the positive pole representing polarized muscle, the negative pole representing depolarized muscle, and the boundary between the two poles corresponding to the activation front. Hence, the local potentials of a depolarizing muscle strip presumably are as follows: the extremity from which depolarization starts would exhibit a purely negative potential since it lies on the negative side of the boundary. Conversely, the end of the strip at which depolarization terminates would

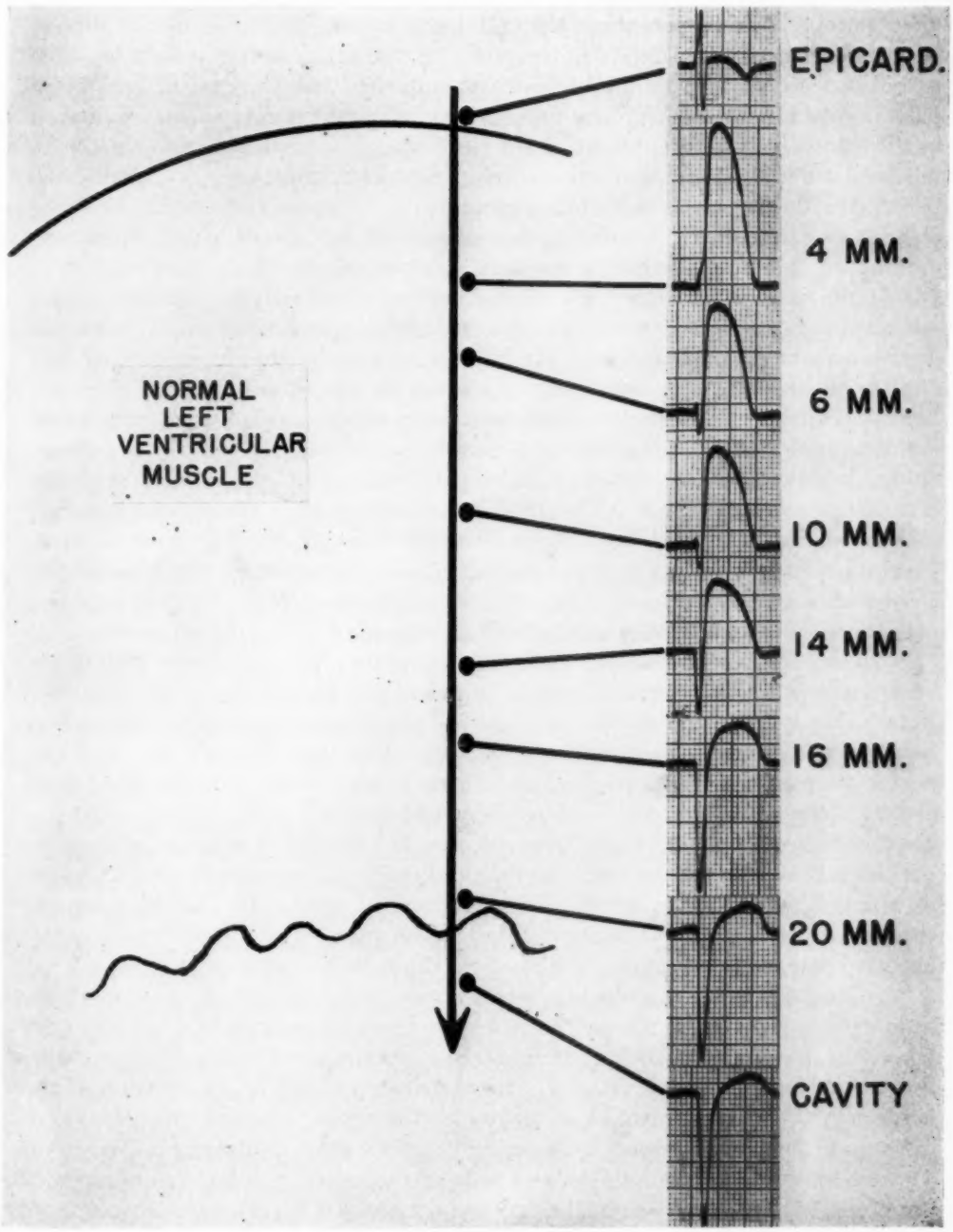

Fig. 6.—Epicardial, intramural, and cavity leads showing intensity of injury currents caused by electrode trauma at varicus levels of the left ventricle. Recorded on the Sanborn direct-writing polyviso at paper speed of 50 mm. per second. Cotton electrode used to obtain epicardial lead elicits no current of injury. Intramural tracings were recorded immediately after insertion of the plunge electrode. Leads from 5, 10, and 15 mm. beneath the surface exhibit RS-T elevation of 25, 21, and 7 mm., respectively, indicating that an approximate inverse relationship exists between the distance from the epicardium and the height of the RS-T segment. When the plunge electrode reaches the cavity, current of injury disappears.

yield purely positive potentials since it faces the positive side of the dipole. Electrodes located between the two ends of the strip would record biphasic potentials consisting of an initial positive component inscribed as the activation front approaches the electrode, followed by a negative component registered as the front passes and recedes from the electrode. The depolarization complexes recorded from the surface of the muscle strip must, therefore, be equally distributed with respect to polarity, predominantly negative deflections occurring in leads from the one-half which is depolarized first and positive deflections predominating in tracings from the one-half which depolarizes last.

If the ventricular wall depolarizes from endocardium to epicardium as an advance of dipoles, the intramural myocardium likewise should display an equal distribution of positive and negative potentials; that is, the innermost one-half of the wall would be predominantly negative, the outermost one-half predominantly positive, and muscle equidistant from the epicardial and endocardial surfaces would exhibit equal phases of positivity and negativity. In the present study, however, essentially negative depolarization complexes were recorded throughout more than two-thirds of the intramural tissue in the ventricles as well as from all depths of the left papillary muscle and from both ventricular cavities. Predominant negativity was registered in unipolar intramural leads whether the chest wall was open or closed. The entire septum also yielded primarily negative deflections, although considerable positivity was recorded as the septal electrode approached the center from the right side. Only in a relatively thin shell of the ventricular wall were predominantly positive depolarization waves obtained. Removal or inactivation of this outer layer of positivity caused the surface deflection to become largely or purely negative, as in intramural leads. That the intramural complexes represented essentially local potentials has been deduced from theoretic considerations and confirmed by experimental tests. Thus, at least a quantitative discrepancy exists between the depolarization process in the ventricular wall during normal sinus rhythm and the hypothetical advance of dipoles in a depolarizing muscle strip. This discrepancy cannot be explained by the lateral passage of the ventricular depolarization wave, since the predominance of negative potentials was found in all sections of the wall from base to apex.

A second possible discrepancy between ventricular excitation and the activation process described in a simple muscle strip concerns the rate of depolarization. Electrical impulses traversing a homogeneous muscle strip presumably would be propagated at a constant velocity. In contrast, the rate of propagation of the ventricular excitation wave, as measured by timing the onset of downstrokes in intramural leads, was found to be considerably slower in the superficial myocardium than in the innermost two-thirds of the wall. Similar results recently were reported by Durrer[19] and Rodriguez and associates.[20] Scher and associates,[10] on the other hand, have obtained evidence that the ventricular depolarization process travels at a constant speed throughout its transmural passage.

Present concepts of the electrophysiology of cardiac muscle are derived from experimental observations of the frog auricle in situ and of ventricular muscle strips suspended in a saline bath. In a previous study,[11] these observations were shown to apply also to the auricles in man and dog. That the mam-

malian ventricles behave electrically in the same manner as a simple muscle strip could not, however, be demonstrated because of the greater complexity of the ventricular musculature. Hence, the assumption that ventricular depolarization occurs as an advance of dipoles from endocardium to epicardium has neither been confirmed nor refuted. It is not improbable that the auricles and ventricles exhibit different modes of depolarization, since the thin auricular myocardium acts electrically as a two-dimensional structure,[11, b] while the thick ventricular wall must depolarize in a three-dimensional manner. The disproportionate negativity and inconstant velocity which were found to distinguish ventricular depolarization may further be related to the presence of the Purkinje system, especially if specialized conducting tissue penetrates a greater proportion of the wall than is generally supposed; under such circumstances, excitation throughout the deeper intramural layers might occur almost simultaneously, so that little or no positive potential would exist in this region. As noted by Wilson and associates,[5] much remains to be learned concerning the ramifications of the Purkinje system and other structural factors which affect the ventricular depolarization process. Finally, on the basis of extensive experimental work, Nahum, Hoff and associates[21-23] have long maintained that ventricular depolarization does not proceed as an advance of dipoles from endocardium to epicardium. This conclusion may be supported by observations described in the present report as well as in subsequent papers on bundle branch block, ventricular extrasystoles, and myocardial infarction.

Depolarization Potentials in the Ventricular Cavities.—In accordance with current electrocardiographic theory, the form of intracavity tracings generally is ascribed to early activation of the septum from left to right, followed by activation of the ventricular walls from endocardium to epicardium. Since the right cavity faces the positive side of the septal activation front and the negative side of the mural activation front, it presumably should yield an initial positive deflection followed by a negative deflection. In the present study, however, plunge electrodes in the right cavity registered pure QS waves in nine of the eleven animals observed. Contrary to current belief, therefore, early activation of the septum from left to right does not necessarily render the entire right cavity positive. Indeed, the following observations suggest that septal depolarization influences the intracavity potential only in a small region near the septal surface, while most of the cavity reflects potentials of the adjacent ventricular wall and papillary muscle:

1. As noted in the present and previous studies, different portions of the same cavity may yield depolarization complexes of different magnitude and configuration. 2. Left cavity leads consistently exhibit pure QS waves. All muscle surrounding the left cavity, including the innermost layers of the left ventricular wall and papillary muscle as well as the left surface of the septum, likewise yield pure QS waves. The cavity QS deflection generally begins at the same instant but is smaller in amplitude than the mural QS from overlying subendocardial muscle. 3. Either an rS or a QS wave may be obtained in the right cavity. Cavity rS waves are simultaneous in onset and similar in configuration to the deflection characteristically recorded from the adjacent right septal surface.

Right cavity QS waves begin simultaneously with the QS waves from adjacent mural myocardium. 4. As reported by previous investigators,[10,17,24,25] an rS wave frequently is registered by catheter electrodes inserted in the right cavity of experimental animals. Similar biphasic complexes commonly occur in right cavity leads obtained from patients by passing a catheter electrode through the right auricle and tricuspid valve. During the present study, however, an initial positive deflection was recorded from the right cavity only in exceptional instances. This apparent discrepancy may be attributed to the fact that catheter electrodes possess a considerably larger recording surface than the plunge electrode. Since the right cavity is extremely narrow, an intracavity catheter electrode probably is often in contact with the septum or at least is sufficiently close to record the initial positive potential of the right septal surface. Intracavity plunge electrodes usually are relatively remote from the septum; consequently, they do not register septal potentials strong enough to affect tracings recorded at the standardization used in the present study. Additional evidence of the difference between intracavity and intraseptal depolarization potentials has been obtained in Sodi-Pallares and associates' study of the septum[26] and in an investigation of bundle branch block to be reported by this laboratory.

The observation that pure QS waves may be recorded from the right cavity serves to explain certain electrocardiographic findings associated with transmural infarction of the right ventricle. During the present study, a QS wave was recorded from the right ventricular surface after the application of formaldehyde. Tracings from various levels of the subjacent wall and cavity exhibited negative complexes identical with the epicardial deflection, indicating that the intracavity potential had been transmitted to the surface through a "hole" of dead muscle. Histologic examination confirmed that the formaldehyde had penetrated the entire thickness of the wall, causing a transmural infarction, but had not affected the septum. If all portions of the right cavity yielded an rS wave, as is generally believed, transmural infarcts of the surrounding wall would be manifested by a similar rS deflection; only if the septum were involved would the surface yield a pure QS complex.

RS-T Segment Displacement in the Clinical Electrocardiogram.—Displacement of the RS-T segment, like the configuration of the QRS complex in unipolar leads, has been attributed to potential differences across an intramural boundary between polarized and depolarized muscle. As defined in accordance with the membrane theory, an injured region is one which polarizes (and probably depolarizes) incompletely, thereby giving rise to a dipole and flow of current at the border of the injury. Wilson and his associates[5] postulate that displacement of the RS-T segment is due to the injury current flowing during electrical systole. Bayley[27] and others attribute RS-T deviation at least partially to the compensating current introduced by the electrocardiograph to neutralize diastolic injury currents. In either event, the direction of current flow is such that electrodes facing the injured zone record an upwardly displaced RS-T segment, while leads facing normal or less severely injured regions show RS-T segment depression.

If the preceding theory is correct, primarily subendocardial injuries should cause downward displacement of the RS-T segment in precordial leads since the

electrode faces the less severely injured zone. This rule would be observed, however, only if the injury effects developed in the subendocardial region were strong enough to markedly affect the distant precordial electrode. In the present experiments, intramural leads recorded directly from subendocardial muscle exhibited much less RS-T segment deviation than leads from subepicardial muscle, indicating that subendocardial trauma elicited relatively weak injury currents. Moreover, several previous investigators[28-30] have encountered difficulty in inflicting subendocardial injuries severe enough to affect the RS-T segment in epicardial, precordial, and limb leads. Although precise quantitative comparisons cannot be made, these experimental findings raise considerable doubt that anoxia of the subendocardial region would produce injury currents strong enough to account for the marked RS-T segment displacement frequently seen clinically, as in angina pectoris and exercise tolerance tests.

A second clinical implication of the preceding experimental observations concerns the RS-T segment deviation observed after coronary occlusion. Serial electrocardiograms of transmural myocardial infarction characteristically display elevated RS-T junctions and segments before the appearance of typical QRS changes. In order to explain this phenomenon, certain workers have hypothesized that a layer of subendocardial muscle immediately adjacent to the ventricular cavity receives blood from supplementary sources when coronary occlusion occurs. The subendocardial layer thus is presumed to undergo less severe anoxia than the overlying myocardium, causing a potential difference and flow of current at the intramural boundary between injured and relatively intact tissue. Since a precordial electrode would face the zone of greater injury, upward displacement of the RS-T segment would be recorded. Wilson and associates[5] initially accepted this hypothesis but later changed in opinion in view of experimental evidence reported by Pruitt and Valencia.[31] Moreover, contrary to the earlier anatomic observations of Gross,[32] recent evidence indicates that anoxia due to coronary occlusion is at least as severe near the ventricular cavity as in the overlying muscle.[33] Thus the original explanation of the direction of RS-T segment deviation following coronary occlusion apparently is no longer tenable. To our knowledge, no alternative explanation which reconciles the electrocardiographic, anatomic, and pathologic findings has been advanced.

Such an explanation may be suggested by the experimental observation that direct trauma elicits less intense injury currents from subendocardial muscle than from subepicardial muscle. In terms of present electrocardiographic theory, this observation indicates that injuries inflicted by the plunge electrode effect a less drastic impairment of polarization (and depolarization) in the subendocardial region than in the subepicardial region. If the assumption is made that the myocardium responds in a similar manner to injuries produced by anoxia, the RS-T segment displacement associated with myocardial infarction may be interpreted as follows: when a coronary artery is occluded, the entire subendocardial region, including the muscle surrounding the ventricular cavity, undergoes at least as severe anoxia as the overlying subepicardium. Nevertheless, as in the experiments, the subendocardial muscle experiences a less drastic impairment of polarization (and depolarization) than the subepicardial muscle,

causing a potential difference between the two regions. Under such circumstances, current flows in the same direction as in primarily subepicardial injury, and the precordial electrode registers an upwardly displaced RS-T segment since it faces the positive side of the dipole. Thus the direction of RS-T segment displacement following coronary occlusion may be related to functional, rather than anatomic or pathologic, differences between the various layers of the ventricular wall.

SUMMARY

1. By means of a specially designed plunge electrode, intraventricular leads were recorded from multiple sites throughout the walls, papillary muscle, septum and cavities of thirty-two dogs during normal sinus rhythm. A series of experiments was performed which established (a) that the presence of the plunge electrode in the myocardium did not alter the normal course of depolarization, and (b) that the depolarization complexes registered by the plunge electrode represented essentially local potentials.

2. Pure QS or rS waves were recorded throughout at least the innermost two-thirds of the intramural myocardium in both ventricles as well as from all levels of the left papillary muscle. Intraseptal leads also exhibited essentially negative deflections, although considerable positivity was noted in the center and right side of the septum. Only the epicardial surface and a thin subjacent layer of the walls yielded predominantly positive depolarization complexes. In general, negative potentials were found to predominate in roughly 80 per cent of the musculature during ventricular depolarization while about 20 per cent of the myocardium was predominantly positive. This observation indicates that the ventricular wall does not depolarize in the same manner as the auricles.

3. Pure QS waves consistently were obtained throughout the left ventricular cavity as well as from all portions of the right ventricular cavity except in the immediate vicinity of the septum. Cavity leads recorded near the right septal surface occasionally displayed a small R wave derived from the initial positivity of the right septal surface.

4. The velocity of the depolarization wave was measured in twenty animals by timing the onset of the downstrokes in intramural leads from multiple depths of the left ventricular wall. As determined by this method, the rate of depolarization appears to be considerably more rapid in the innermost two-thirds of the wall than in the superficial layers.

5. Currents of injury, manifested by RS-T segment elevation, always occurred for a brief period following the introduction of the plunge electrode into the myocardium. The RS-T segment deviation was markedly less in subendocardial leads than in subepicardial leads, indicating that subepicardial muscle characteristically is capable of producing more intense injury currents than are the deeper layers of the myocardium.

6. The observed weakness of subendocardial injury currents in experimental animals suggests that the downward RS-T segment deviation, which is

seen clinically in angina pectoris, is not attributable to subendocardial anoxia as is generally believed. On the basis of the same experimental observation, a new theory concerning the cause of RS-T segment elevation following coronary occlusion is proposed which appears to reconcile apparent discrepancies among the electrocardiographic, anatomic, and pathologic findings.

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VENTRICULAR PREMATURE SYSTOLES WITH POSTPONED COMPENSATORY PAUSE

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IN A previous report from this department[1] a phenomenon in association with interpolated ventricular premature systoles was described. A case was presented in which such interpolation affected auriculoventricular conduction not only of the first postextrasystolic beat but also of the second one, causing P-R prolongation or even failure of the ventricle to respond to the sinus impulse following the postextrasystolic impulse. The purpose of the present report is to present electrocardiograms of three additional patients showing the latter phenomenon and to propose a term for the unusual disturbance.

DESCRIPTION AND INTERPRETATION OF ELECTROCARDIOGRAMS

The electrocardiograms of the cases discussed are shown in Fig. 1. Records *A* and *B* were obtained on a 63-year-old patient with arteriosclerotic heart disease. The spacing of the P waves is regular. In *A*, the P-P interval is best seen at the end of the record. The second P wave is hidden in the QRS complex of a ventricular premature systole, the third P wave is superimposed on the T wave of the postextrasystolic beat, the end of the fifth P wave can be identified immediately following the W-shaped QRS complex of a ventricular premature systole, and the sixth P wave is again superimposed on the T wave of the postextrasystolic beat. In *B*, the fourth and ninth P waves are hidden in the QRS complexes of a premature systole, and the fifth and tenth P waves are superimposed on the T wave of the postextrasystolic beat. The ventricular complexes following the ventricular premature systole in both *A* and *B* are identical in contour with the sinus beats and are interpreted as delayed ventricular responses to the sinus P waves hidden in the bizarre QRS complex of the premature systole; hence, there is interpolation of the premature systole. As a result of the P-R prolongation (0.32 sec. to 0.46 sec.) of the postextrasystolic beat the subsequent sinus impulse reaches the auriculoventricular junction during its absolute refractory period and fails to elicit a ventricular response. Thus, a postponed compensatory pause occurs after a sinus beat instead of following the premature systole.

Record C, taken on a 68-year-old patient with chronic coronary insufficiency, shows four ventricular premature systoles the third of which is followed at a short distance by a ventricular complex of supraventricular contour coinciding with a sinus P wave (merged with its R′) which is not followed by a ventricular response. This is another example of a ventricular premature systole with postponed compensatory pause. The P-R of the postextrasystolic beat measures 0.68 second.

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Record *D*, obtained on a 54-year-old patient with arteriosclerotic heart disease, shows a regular sinus rhythm with two ventricular premature systoles. The third, fourth, and sixth sinus P waves cannot be identified; they must be hidden in a ventricular complex since the auricular rhythm remains undisturbed. The first premature systole is interploated; however, the marked P-R prolongation (0.56 sec.) of the postextrasystolic beat is responsible for nonconduction of the subsequent sinus impulse. Again, the compensatory pause following the ventricular premature systole is postponed.

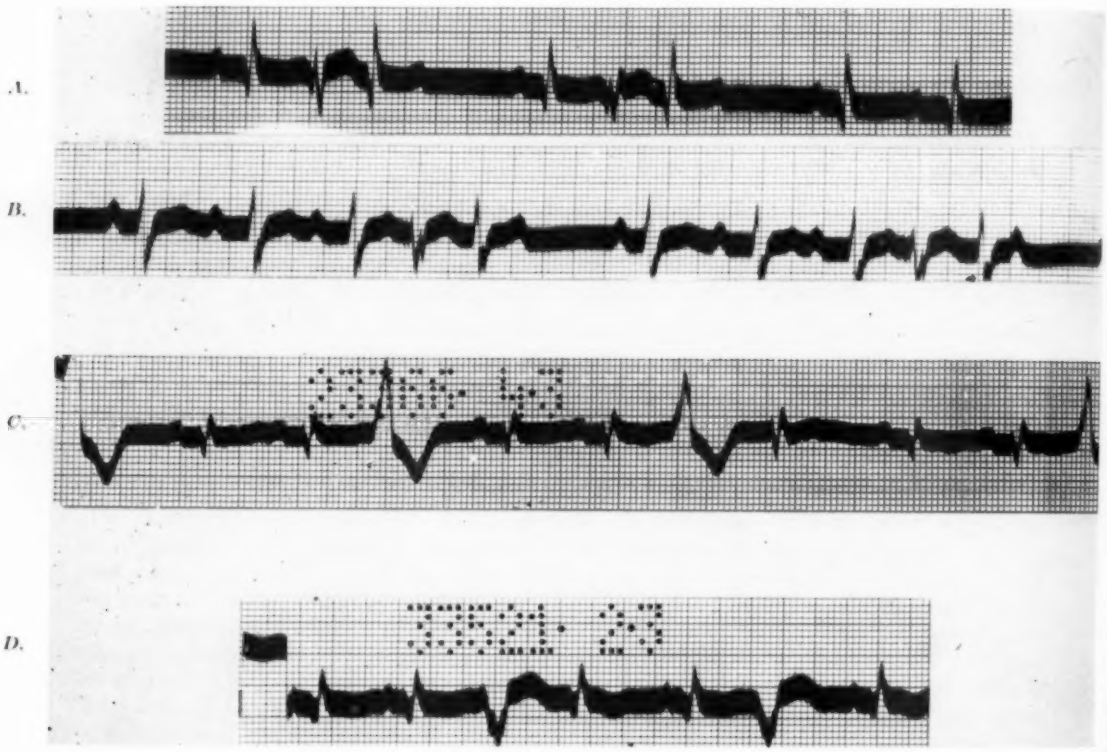

Fig. 1.—Electrocardiograms obtained in three patients exhibiting ventricular premature systoles with six instances of ventricular premature systole, with the phenomenon called postponed compensatory pause. In each case it is the marked P-R prolongation of the first postextrasystolic beat which is responsible for the failure of the next subsequent sinus impulse to elicit a ventricular response. Records A and B are Leads I and II of the same case, records C and D are Lead III of two other cases. Discussed in text. (Record C from Katz, Electrocardiography, Lea & Febiger, 1946.)

In Table I, the data of all three cases are tabulated concerning the rate and the duration of the P-R interval of the sinus beats preceding the ventricular premature systoles, the coupling of the premature systoles, the R-P distance and P-R interval of the first postextrasystolic beat as well as the R-P distance preceding the second postextrasystolic P wave. The records differ in rate and auriculoventricular conduction time of the sinus beats; the only feature in common is the occurrence of the premature systole at such a time that the inscription of the P wave of the postextrasystolic beat coincides with that of the QRS complex of the premature systole.

TABLE I. SUMMARY OF PERTINENT DATA

CASE IN FIG. 1	SINUS RATE (BEATS/MIN.)	P-R INTERVAL OF PRE-EXTRASYSTOLIC BEATS (SEC.)	COUPLING OF EXTRASYSTOLE (R-R INTERVAL) (SEC.)	RELATION OF R-P TO P-R INTERVAL OF FIRST POST-EXTRASYSTOLIC BEAT		R-P INTERVAL PRECEDING SECOND POST-EXTRASYSTOLIC
				R-P (SEC.)	P-R (SEC.)	P (SEC.)
A	94	0.24	0.36	0.00	0.38	0.30
	94	0.20	0.40	0.04	0.32	0.30
B	94	0.26	0.38	0.00	0.42	0.26
	96	0.26	0.38	0.00	0.46	0.22
C	88	0.20	0.46	0.00	0.68	0.04
D	103	0.14	0.48	0.00	0.56	0.00

COMMENT

The question obviously arises whether the ventricular beat, resembling the sinus beats in contour, which follows the premature beat of bizarre contour might also be an ectopic beat rather than a sinus beat. This would mean that two premature systoles occur in succession, the first ventricular, the second auriculoventricular nodal in origin. The complete absence of single nodal premature systoles or of nodal premature systoles initiating multiple premature systoles would be against this interpretation. However, this argument is not entirely convincing since the premature systoles illustrated, which are regarded as being ventricular in origin, may be nodal in origin with aberrant ventricular conduction.[2] Our interpretation of the arrhythmia as associated with a ventricular premature systole with a postponed compensatory pause is based upon the well-known effect of an interpolated premature systole in prolonging the P-R interval of the postextrasystolic beat when the sinus impulse comes very soon after the premature beat. When the sinus impulse comes early enough and the sinus rate is relatively rapid, then the P-R of the postextrasystolic beat may be prolonged enough to cause the ventricular response to come so late as to make the second postextrasystolic sinus impulse arrive in the absolute refractory phase of the first postextrasystolic beat. Hence, the occurrence of the postponed compensatory pause implies a physiologic phenomenon determined by the refractory phase of the junctional tissues. This is confirmed by the actual observation of typical interpolated premature systoles as well as interpolated premature systoles with prolongation of the first and second postextrasystolic P-R interval in a patient exhibiting the phenomenon under discussion.[1]

In ventricular or nodal premature systoles, the phenomenon of premature systoles with postponed compensatory pause is intermediate between the premature systole with fully compensatory pause and the interpolated premature systole. It resembles the effect of a typical premature systole in that the number of ventricular beats is not increased by its occurrence, and at the same time it resembles an interpolated premature systole in that the postextrasystolic sinus

impulse elicits a ventricular response. We propose the term premature systole with postponed compensatory pause to indicate the mechanism of this infrequent disturbance.

SUMMARY

Several examples of a physiologic phenomenon accompanying ventricular premature systoles are presented and analyzed. The term postponed compensatory pause is proposed for this infrequent disturbance.

The author is indebted to Dr. Louis N. Katz for his valuable criticism.

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ARCHITECTONICS OF THE HEART

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THE principal function of the heart is a mechanical one and, therefore, to understand heart function one must know its mechanical or three-dimensional architecture. There have been, however, few systematic studies of the structure of the heart from this functional point of view. Conventional techniques for the pathologic examination of the heart cannot give this type of information because in them the heart is incised and laid out flat—reducing it to a two-dimensional structure—before measurements are made. Such aspects as the directions and sizes of inflow and outflow tracts of the two ventricles, the angles which the tricuspid and mitral valves make with the directions of the inflow tract of the ventricles, and the changes in the direction of the aorta before it emerges from the epicardial fat are important in the function of the heart and often undergo marked and specific alterations with the development of certain heart diseases. As will be seen, these alterations in the functional architecture of the heart sometimes are responsible for certain of the clinical features of heart disease.

METHODS

In this course of other studies a simple method for dissecting the heart was devised which made it possible to study its three-dimensional architecture. On removal of the heart, the atria and ventricles are gently packed with formalin-soaked gauze to restore their contours, and the heart is then immersed in formalin before further dissection. The coronary vessels may be injected with formalin to improve fixation. Following fixation, the atria are opened, inspected, and dissected away at their ventricular attachments. Then, after appropriate examination, the entire epicardial fat, connective and vascular tissues are carefully dissected away, leaving only ventricular myocardium. This is important because the layer of fat overlying the base of the heart may exceed two centimeters in thickness in the normal heart, obscuring the right ventricular outflow tract and the root of the aorta. At this stage of the dissection, the planes of the mitral and tricuspid orifices in relation to the direction of the inflow tracts of the two ventricles are studied; the diameters of the orifices are measured; and the capacities of the right and left ventricles are determined by measuring the amount of water each will hold, in this way roughly quantitating the presence and degree of dilatation of the ventricles at the time of death.

Next, the free wall of the right ventricle is dissected away at its septal attachments. These two parts of the ventricular myocardium — the free wall of the right ventricle and the left ventricle plus septum — are separately weighed. These weights are much more valuable for evaluating the presence and degree of ventricular hypertrophy than is the gross weight of the intact heart. It is often not appreciated that the ventricular myocardium accounts for only 50 per cent

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of the total heart weight and may vary from 30 per cent to 90 per cent in normal subjects. On the basis of Müller's measurements in more than 1,100 autopsies and those of others since him, the normal weight of the free wall of the right ventricle is considered to be 40 to 60 grams and the normal weight of the left ventricle and septum 140 to 180 grams.[1,2]

Upon removing the free wall of the right ventricle, the tricuspid and pulmonary valves are examined and the inflow and outflow tracts of the right ventricle are studied. With the septum exposed, the relationships of the right and left ventricles to one another and their relative sizes are apparent. Next, the inflow and outflow tracts of the left ventricle are examined. This is done by making a longitudinal incision completely through the left ventricle in a plane which is perpendicular to the anterior or aortic leaflet of the mitral valve. This divides the left ventricle in half along the pathways of the inflow and outflow tracts. The relative lengths and diameters of the tracts are measured, and the angles which the planes of the mitral and aortic rings make with the two tracts are studied. The extent to which the various parts of the chamber participate in dilatation and the distribution of hypertrophy along the walls of the ventricle are studied. The aortic and mitral valve leaflets, the chordae and papillary muscles are examined, and the membranous portion of the septum can be seen by transillumination at the base of the aortic ring.

The removal of the epicardial fat and connective tissue may be facilitated by immersing the heart in slightly acidified water and bringing it to a boil before dissection. This makes for a "cleaner" specimen and one that lends itself to clearing or dehydrating for demonstration purposes. However, the weights and measurements of the heart may be reduced 30 to 50 per cent by this procedure.

The technique for collecting data in this study consisted of recording spatial measurements and angular relationships of the inflow and outflow tracts, the chamber orifices, and the valve components of the two ventricles. Ratios among certain of these data were studied, giving a quantitative and objective framework on which to reconstruct changes which had taken place in the three-dimensional structure of the heart in various forms of heart disease. Although the circumstances of the study did not permit the study of a large enough number of hearts to justify publishing these data in detail, certain types and directions of structural abnormality occurred regularly in specific forms of heart disease, and these observations form the basis for the present report. It is hoped that others better equipped for this type of study will undertake a more comprehensive and detailed study of these mechanical and spatial characteristics of cardiac pathology.

THE NORMAL HEART

Although the heart consists of two pumps lying side by side, the right and left ventricles, these two pumps are strikingly different structurally. For example, the flow of blood through the right ventricle is unidirectional; that is, blood enters at one orifice and leaves at another, with the inflow and outflow tracts forming an angle of 90° with each other. On the other hand, in the left ventricle, flow is essentially bidirectional, with the blood entering and leaving from the same orifice; for only a thin membrane, the anterior leaflet of the mitral valve, separates the mitral and aortic orifices of the left ventricle. This difference is illustrated in Fig. 1.

The spatial relationships of the various component parts of the normal heart are shown schematically in Fig. 2. In this illustration an anteroposterior view and a right and left lateral view of the heart are shown at three stages of dissection: upper, the intact heart; middle, the ventricular heart; and lower, the left ventricle and the septum indicated by the remnant ridge of the right ventricle where its free wall was dissected away from the left ventricle.

Several features regarding the position in the body of the heart and its components are shown here which deserve emphasis; however, it is well to remember

that these studies were done in supine subjects, and the relationships are somewhat different in the erect position. In the chest roentgenogram and even at post-mortem examination the atria and fat at the base of the heart hide the root of the aorta and only its superiorly extending portion can be seen. Accordingly, it is commonly thought that the left ventricle is suspended vertically from the aorta with the aortic orifice of the ventricle facing superiorly. However, as can be seen in the illustration and also in Fig. 4, this is not the case. The left ventricle has a relatively horizontal position, and the mitral-aortic orifice of the ventricle faces more rightward than superiorly. The aorta makes two significant changes in direction before it emerges from the epicardial fat at the base of the heart. As it leaves the outflow tract of the left ventricle, it turns anteriorly to ride against the conus or outflow tract of the right ventricle for a distance of about four centimeters. This angulation represents a change in direction of about 60 degrees from the direction of the left ventricular outflow tract. Then the aorta bends superiorly, which represents another change in direction of about 60 degrees, before it emerges from the epicardium. In other words, in the supine position the direction of the extracardiac portion of the aorta is nearly 90 degrees from the direction of the outflow tract of the left ventricle.

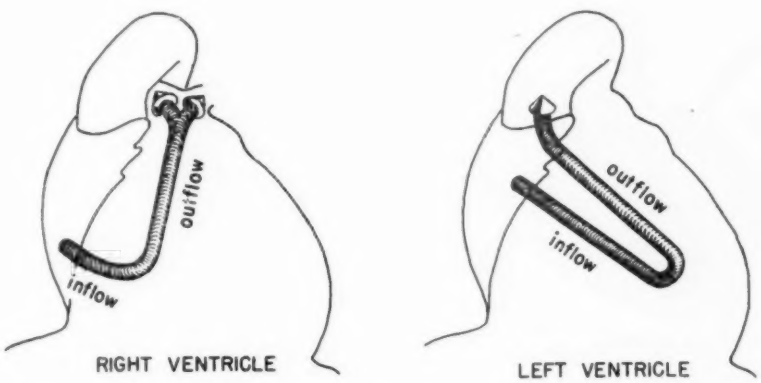

Fig. 1.—The directions of the inflow and outflow tracts of the right and left ventricles from the frontal view. From Grant, R. P.: Circulation **7**:897, 1953 (Fig. 6), Grune & Stratton, Inc.

This early rightward direction of the aorta explains why, in the "uncoiling" of the aorta in hypertension, the ascending portion of the aorta tends to shift to the right, coming to overlie the hilus of the right lung in roentgenograms. In addition, it may explain the rotation of the ballistocardiographic vectorgram in older age groups,[3] for, with the development of atherosclerosis and consequent loss of elasticity of the aorta in older subjects, the force of cardiac ejection will be more completely communicated to the body as a rightward force than it is in younger subjects.

Another anatomic feature of the heart to note in this illustration is the location of the left atrium. Although it is often considered to lie on the posterior surface of the heart, it can be seen that the mitral orifice faces more to the right

than posteriorly and that the left atrium actually lies to the right of the left ventricle rather than behind it. This explains why in mitral stenosis the dilating left atrium enlarges to the right, often extending beyond the right atrium in the frontal roentgenogram. The esophagus lies behind the left atrium and may be deviated to the right, the left, or posteriorly by this atrial dilatation.

It will be noted that the bifurcation of the pulmonary artery lies over the sulcus between the left atrium and left ventricle with the right branch of the pulmonary artery passing over the left atrium and the left branch passing over

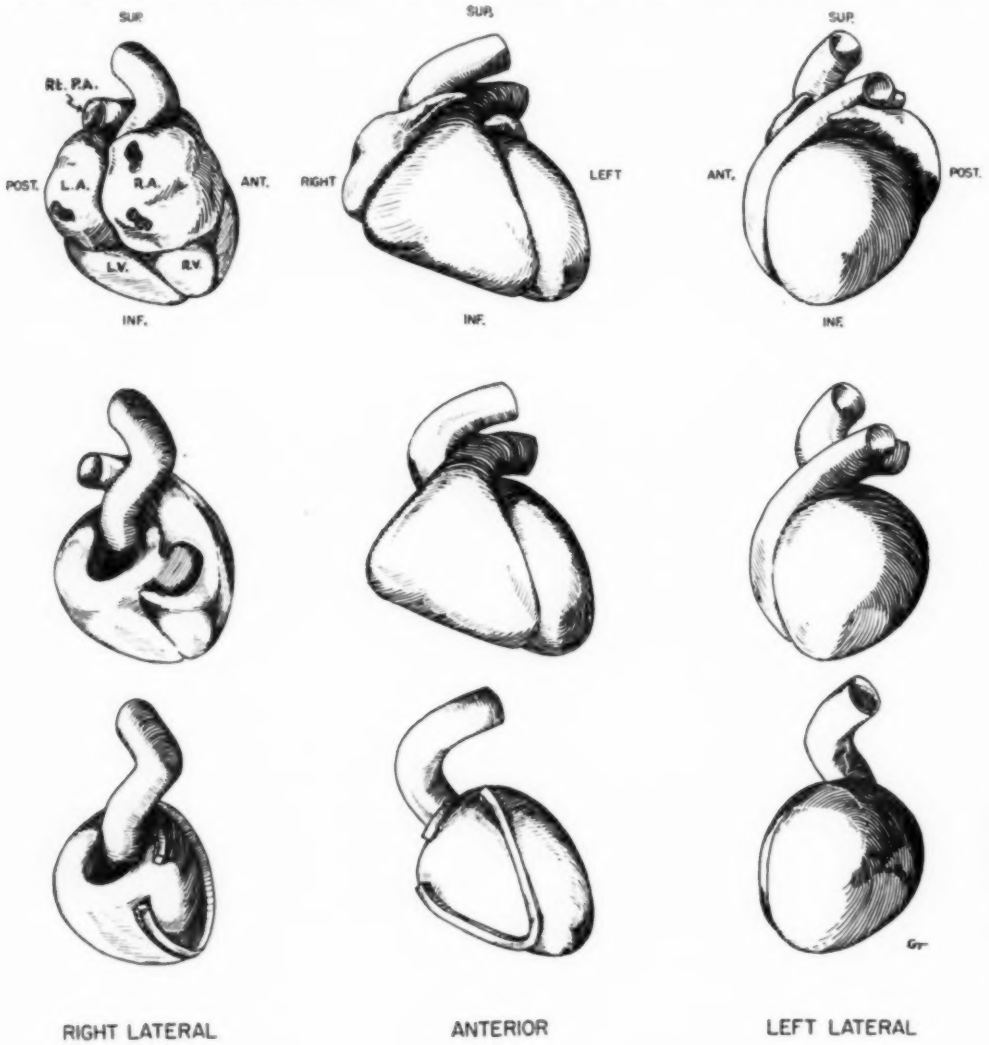

Fig. 2.—The normal heart showing the relationships of the various chambers to one another as they lie in the chest. The drawings were made from photographs of a schematized clay model which was constructed from photographs of nine normal hearts dissected by the method described. Upper row: the intact heart with only epicardial fat and connective tissue removed. Middle row: ventricular heart from the same three views, the two atria having been removed. Bottom row: the left ventricle and aorta from the same three views, the free wall of the right ventricle having been removed along the pathway where its fibers interdigitate with the fibers of the left ventricle.

the left ventricle. Because of this, marked dilatation of the left atrium is more likely to compress the right branch of the pulmonary artery than the left. This has been suggested as the explanation for the greater frequency of pulmonary infarction and pleural effusion in the right side of the chest than on the left in patients with congestive heart failure and mitral stenosis.[4,5]

It will be noted also that the right ventricle is anterior to the left ventricle. Indeed, it would be more consistent with the anatomic facts to call them an "anterior" and a "posterior" ventricle than a "right" and "left" ventricle. The plane of the interventricular (and interauricular) septum is relatively parallel with the frontal plane of the body. Thus, what is called the "posterior" part of the heart in usual cardiologic nomenclature (where the "posterior" sulcus lies and where "posterior" myocardial infarctions occur in electrocardiographic nomenclature) is actually the inferior surface rather than the posterior surface of the heart. Myocardial infarctions involving this region of the septum and adjacent left ventricle are more accurately termed "inferior" or "diaphragmatic" than "posterior," for truly posterior myocardial infarctions have quite different electrocardiographic characteristics from infarcts of the diaphragmatic portion of the left ventricle.

The interventricular septum is not an independent muscle structure separating the two ventricles but is structurally an integral part of the left ventricle.[9] As shown in the figure, it is that region of the left ventricle to which the free wall of the right ventricle attaches. This septal portion of the left ventricle accounts for only about 60 degrees of the circumference of the ventricle. The remainder, called the "free wall" and often considered to be a "lateral" part of the left ventricle, actually includes about 300 degrees of the ventricle and faces superiorly, posteriorly, and inferiorly, a fairly large portion of it resting on the diaphragm.

The extent to which the heart may undergo clockwise or counterclockwise rotation on its long axis as a result of ventricular hypertrophy or dilatation has been recently studied. Exacting techniques were used for defining the precise lie in the body of the various regions of the heart in a large number of normal and abnormal subjects, and the results have been reported in detail elsewhere.[6] It was found that while the heart might shift superiorly or inferiorly with ascites, obesity, etc., it did not rotate on its long axis more than 20 degrees as a consequence of even the most marked hypertrophy, and there was little variation in the degree of anterior or posterior tilt of the heart among these cases. The reason for the relatively fixed position of the heart in the body is that the ventricular myocardium has its origins and insertions in the collagenous rings of the four orifices of the ventricular heart and, therefore, can only rotate if the rings also rotate. These dense rings are tightly bound to one another, forming what has been called the "skeleton" of the heart.[7] The great vessels attach tangentially to these rings, in this way anchoring the "skeleton" and preventing rotation from taking place.

There is a simpler though less exact method for identifying the position of the heart than was used in this study. The portion of the heart which rests on the diaphragm tends always to have a particularly flat surface, even in the presence of marked ventricular hypertrophy or dilatation. Accordingly, one need

only look for the conspicuously flat surface of the heart and this will be the diaphragmatic (or inferior) surface. The diaphragmatic surface can also be identified by locating the posterior sulcus of the heart, the fatfilled crevice which marks the inferior margin of attachment of the free wall of the right ventricle to the left ventricle and which contains the descending branch of the right coronary artery. This sulcus always lies on the diaphragmatic surface of the heart.

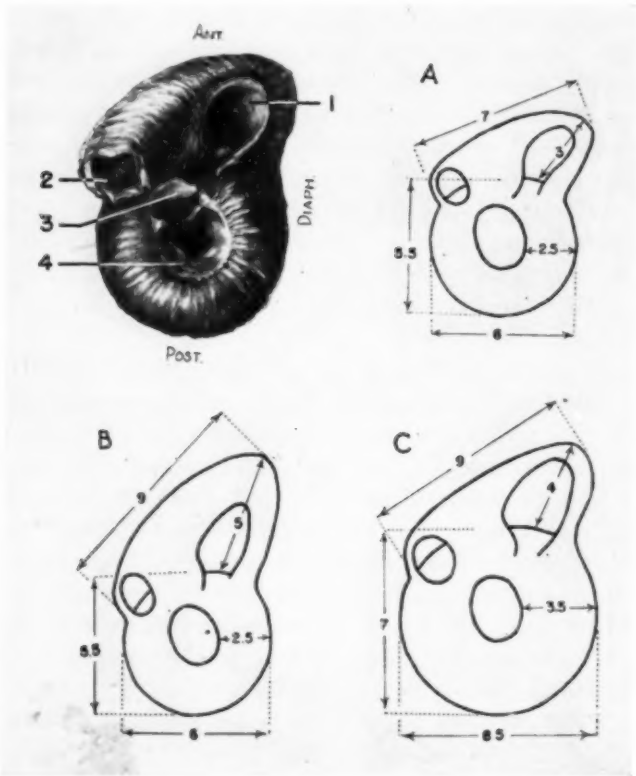

Fig. 3.—The base or "skeleton" of the ventricular heart showing its position in the body and the changes produced by heart disease. *1*, tricuspid orifice; *2*, pulmonary artery orifice; *3*, aortic orifice; *4*, mitral orifice. Drawn to the same scale are: *A*, the normal heart; *B*, the heart with right ventricular hypertrophy and dilatation; and *C*, the heart with left ventricular hypertrophy, with representative measurements in centimeters from a small group of cases of each.

A useful perspective from which to study the ventricular heart for the effects of hypertrophy or dilatation is in the plane of its "skeleton"; that is, to look at the ventricular heart from the patient's right side. In this view all four orifices and the muscle mass of both the right and the left ventricle can be studied. This is illustrated in Fig. 3 which shows a normal heart drawn in detail and then, schematically and to the same scale, the normal heart *A*, the heart with right ventricular dilatation and hypertrophy *B*, and the heart with left ventricular hypertrophy *C*.

It will be noted that the skeleton itself is little altered by heart disease, only the thinner tricuspid ring showing much variation in diameter. Even in left ventricular hypertrophy the diameter of the mitral-aortic orifice is not increased

until the hypertrophy becomes extreme. The four orifices are tightly bound to one another, and there is little change in their angular relationship to one another in even the most marked right or left ventricular disease.

It can be seen that the three parts of the cardiac skeleton which most commonly undergo calcification (the mitral leaflets, the posterior rim of the mitral ring, and the aortic cusps) lie practically in the same plane and are extremely close to one another. This explains why identifying the location of intracardiac calcification by roentgenogram is often so difficult. In the frontal view the three structures tend to overlie one another, and the best view for differentiating them fluoroscopically is the right oblique view, essentially the same view as this illustration. However, movement of the calcification with cardiac systole is more difficult to recognize in this view.

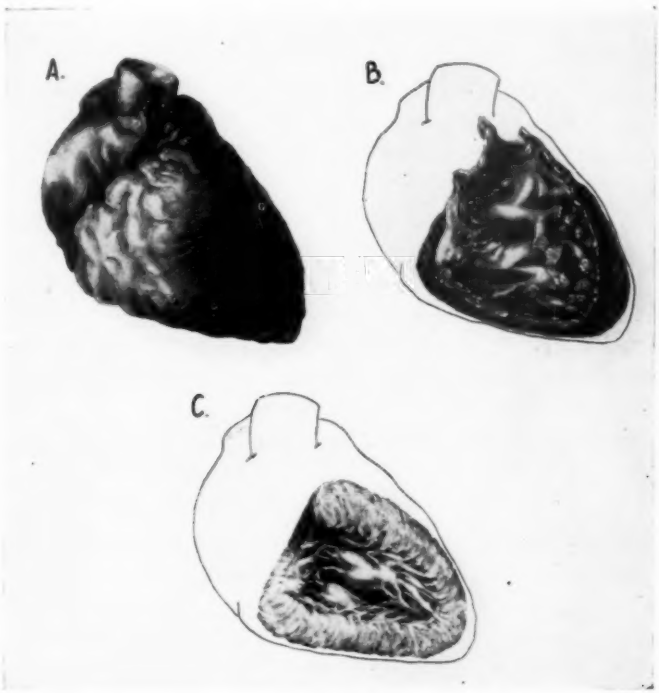

Fig. 4.—The normal heart at three stages of dissection viewed from the frontal aspect as it lies in the body. *A*, the intact heart; *B*, the ventricular heart with the free wall of the right ventricle removed; and *C*, cross section of the left ventricle exposing the inflow tract.

It will be noted that the mitral-aortic orifice appears to be eccentric in location in all three diagrams; that is, the septal portion of the left ventricular wall appears to be thinner than other portions. This is not actually the case but appears so because the inner surface of the left ventricle is concave at its posterior (mitral) margin but is convex at its anterior (aortic) margin. The reason for this is that the aorta arises from the latter part of the left ventricle, curling anteriorly against the free wall or outflow tract of the right ventricle. This difference in contour between the anterior and posterior lips of the left ventricle is more easily seen in longitudinal sections of the left ventricle, as shown later in Fig. 12.

The relationships of the various parts of the heart are shown from another perspective in Fig. 4. A normal heart is shown from the frontal view in exactly the position it had in the body, as determined by the method mentioned earlier.[6] First is shown the intact, undissected heart. In the second drawing the atria, epicardial fat and connective tissue, and the free wall of the right ventricle have been removed. It will be noted that the septum is relatively parallel with the frontal plane of the body and only a small part of the free wall of the left ventricle can be seen in this view. The concave contour of the medial wall of the outflow tract of the right ventricle is shown, where it is molded tightly against the early, anteriorly directed portion of the root of the aorta. It can be seen that the pulmonary artery has a nearly complete posterior direction from the pulmonic valve to its bifurcation. Regarding the internal structure of the right ventricle, the trabeculae carnae connecting the floor or septal wall of the ventricle with its free wall (transected in this illustration) occupy the lateral region of the chamber, and the outflow tract of the right ventricle occupies the medial or basal region. The number and density of these trabeculae vary markedly from heart to heart, and the horizontal ridge at the beginning of the outflow tract (the crista supraventricularis) is the only relatively constant feature of the architecture of the floor of this ventricle.

In the third drawing the left ventricle of this heart is transected behind the anterior leaflet of the mitral valve so that only the inflow tract can be seen. The posterior leaflet of the mitral valve and the two principal papillary muscles are shown. The drawing demonstrates well the relatively horizontal lie of the left ventricle and the nearly 90-degree difference in direction between the direction of the left ventricle and the ascending aorta. It will be noted that the apical wall of the left ventricle is slightly thinner than the lateral walls. Similar drawings of the heart in mitral stenosis and in left ventricular hypertrophy are shown in Figs. 8 and 10.

RIGHT VENTRICULAR HYPERTROPHY

That right ventricular hypertrophy often accompanies left ventricular hypertrophy has been long recognized. It has usually been attributed to the effects of the congestive heart failure that often develops in patients with left ventricular hypertrophy[1,2,8] However, in eighteen hearts with marked left ventricular hypertrophy in the present study, the free wall of the right ventricle was found to be greater than normal in weight in all patients, whether or not congestive heart failure had been present. There is a satisfactory anatomic reason why right ventricular hypertrophy regularly accompanies marked left ventricular hypertrophy. Since the septum consists almost entirely of left ventricular fibers,[9] any process which increases the size of the left ventricle increases the area of the septum. This means that the septal surface of the right ventricle is automatically increased whenever there is left ventricular hypertrophy, and the free wall of the right ventricle is increased in size, correspondingly. This is illustrated in Fig. 5. The two lower left ventricles are from normal hearts while the two upper left ventricles are from patients who had left ventricular hypertrophy without congestive heart failure. It can be seen that the right ventricular surface of the septum was increased in area corresponding with the degree of left ventricular hypertrophy.

This right ventricular hypertrophy secondary to left ventricular hypertrophy may not be accompanied by a significant increase in the capacity of the right ventricle. The reason for this is that the dense network of trabeculae carnae connecting the floor (septal surface) and free wall of the right ventricle is also hypertrophied, as can be seen in the illustration. These hypertrophied trabeculae more completely fill the lateral compartment of the right ventricle so that the outflow tract becomes confined to a relatively narrow channel along the medial border of the right ventricle and, therefore, remains relatively normal in volume. This hypertrophy of the trabeculae may be so marked that it is extremely difficult to find the septal attachment of the free wall of the right ventricle, and it is hard to see how any blood could have penetrated into this region of the ventricle.

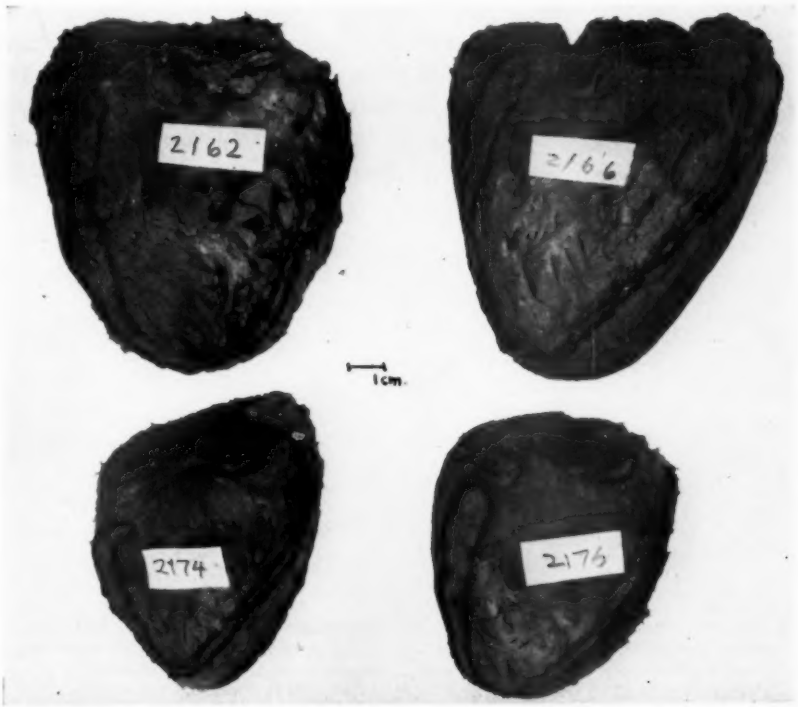

Fig. 5.—The relationship between the area of the septum and the size of the left ventricle. The two upper hearts are instances of left ventricular hypertrophy, while the two lower hearts are normal. The inner and outer margins of the free wall of the right ventricle where it was dissected away from the left ventricle were marked with indelible ink before photography and later retouched.

If for one or another reason congestive heart failure or cor pulmonale should develop in such a heart, the anatomically hypertrophied right ventricle will now become dilated, and this is identified by measuring the capacity of the chamber. The anatomic changes which take place with right ventricular dilatation appear to be the same, whether or not the left ventricle is hypertrophied: the network of trabeculae connecting the septum and the free wall becomes less dense by virtue of attenuation and the entire network appears to shift laterally. Thus,

more and more of the septal surface of the right ventricle surface becomes converted into an effective floor for inflow and outflow tracts. The way in which this takes place is obscure; whether the more medial trabeculae vanish or whether the origins and insertions of the trabeculae shift leftward is not known. In any case, by virtue of this change in the effective surface area of the chamber, more and more becoming available for flow, the capacity of the ventricle may be as much as doubled with little apparent change in the outer contour of the heart.

Further increases in the size of the right ventricle must take place by distention of the free wall because the septal surface of the chamber is fixed by the size of the left ventricle. With dilatation, the first change is elongation of the inflow tract anteriorly, as illustrated in Fig. 3, *B*. With further dilatation the ventricle "bulges" over the septum, hiding the left ventricle in the frontal view. The "bulging" may be so marked at the apex of the right ventricle that the heart comes to have a "double apex," that is, separate apices for the right and left ventricle.[10] This is commonly seen in advanced mitral stenosis and is illustrated in the second drawing of Fig. 8 which shows the ventricular changes in mitral stenosis. The double apex may not be recognized roentgenographically or even when looking at the undissected heart at autopsy, for there is usually a marked increase in epicardial fat between the two apices, rounding off this region of the heart.

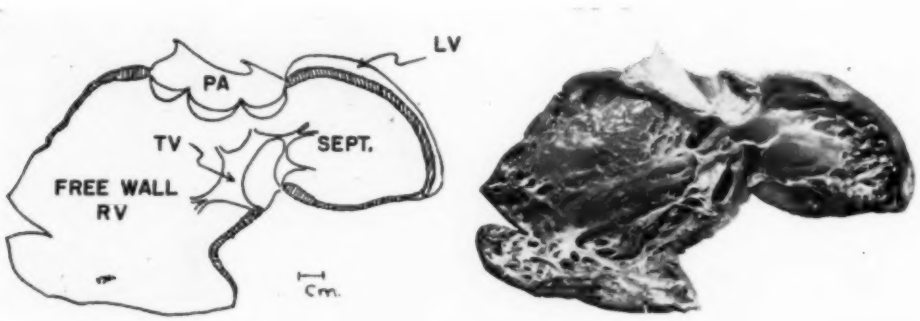

Fig. 6.—Enormous hypertrophy and dilatation of the right ventricle in a case of Lutembacher syndrome. The free wall of the right ventricle has been reflected from the remainder of the heart near the septum, and the incision made for this is indicated by diagonal shadings in the diagram. *PA*, pulmonary artery; *LV*, left ventricle; *TV*, tricuspid valve (J.H.H. No. 22954).

The outflow tract of the right ventricle also becomes dilated and "bulges" beyond the septal margin. Here, too, epicardial fat accumulates, occasionally having a depth of nearly two centimeters, and molding the dilated outflow tract to the contour of the left ventricle. The added epicardial fat in this region often accounts for the remarkable width of this region of the heart by roentgenogram in certain cases of right ventricular hypertrophy and dilatation.

The most marked instances of right ventricular hypertrophy and dilatation occur in adults with congenital heart disease. In Fig. 6 is shown the most striking example of right ventricular dilatation in the present series of cases and one of the largest reported in the literature. This heart was obtained from a young adult

who died following two years of progressive congestive heart failure associated with the Lutembacher Syndrome (mitral stenosis with atrial septal defect).* The capacity of the right ventricle was nearly 300 c.c., almost five times the normal right ventricular capacity. In the photograph the right ventricle has been opened along its widest margin. The reflected portion of the free wall is more than 100 sq. cm. in area while the septal surface measures less than 25 sq. cm. in area, illustrating the extent to which the right ventricle "bulged" over the left ventricle largely hiding it.

Similarly, the most striking instance of right ventricular hypertrophy in the present series was also encountered in an adult with congenital heart disease. In this case,† a 30-year-old woman with an interventricular septal defect and pulmonic stenosis, the right ventricular free wall measured 2.0 cm. in thickness, while the left ventricular wall measured 1.5 cm. in thickness. There is no previously reported case of an adult heart where the right ventricle was thicker than the left ventricle. The right ventricle was not dilated in this case, perhaps because there had been no congestive heart failure, the patient dying of miliary tuberculosis.

The reason why right ventricular hypertrophy and dilatation may be more marked in congenital heart disease than in acquired heart disease is probably related to the fact that myocardial mitoses may be seen as late as the first few months after birth.[11,12] Therefore, abnormalities of cardiac function at birth will tend to be accompanied by considerably more hyperplasia of myocardial fibers than will the same abnormalities acquired later in life. This would lead to a greater degree of hypertrophy at later stages of the illness. That this might be the case in these two hearts was demonstrated by crude fiber counts of the free wall of the right ventricle in both instances. The volume of the free wall was measured and the number of fiber layers from inner to outer surface was counted at several regions of the wall. By such an admittedly crude method of calculation it was apparent that there were several times the normal number of myocardial fiber "units" in the free wall in these two hearts. In two instances of acquired cor pulmonale with marked right ventricular hypertrophy the number of fiber "units" in the free wall was not greatly different from that in normal hearts.

ARCHITECTURAL CHANGES OF THE LEFT VENTRICLE IN MITRAL VALVE DISEASE

While clinicians generally believe that mitral insufficiency leads to left ventricular hypertrophy and in "pure" mitral stenosis the left ventricle is normal or less than normal in weight, the pathology literature is far from in agreement on this subject.[13,14] There are even reports of "pure" mitral stenosis producing hypertrophy of the left ventricle; the authors explain this by postulating increased diastolic work by the left heart, actively aspirating blood through the stenosed mitral valve during diastole.[15] Probably the principal reason for the inconsistent

*No. 22954 Department of Pathology Teaching Collection, Johns Hopkins University Medical School.

†From the Teaching Collection, University of Maryland Medical School.

findings in these studies is that there is no satisfactory method for determining at post-mortem whether the stenosis or the insufficiency is the more important physiologic lesion, and the differentiation clinically is even more difficult.

In 1929 Kirch, who was the first to study the functional anatomy of the heart and introduced the terms "inflow tract" and "outflow tract," pointed out that in nearly all hearts with mitral stenosis the posterior wall or inflow tract of the left ventricle was markedly shortened, whether or not accompanied by mitral insufficiency.[16] This observation has been largely neglected in this country. In the present series of cases, eleven hearts with essentially uncomplicated mitral valve disease have been studied and Kirch's findings largely substantiated. This alteration is illustrated in Fig. 8 which is a drawing of the heart with mitral stenosis and is to be compared with the normal heart in Fig. 4. The shortening of the posterior wall can often be seen in the roentgenogram when the mitral ring is calcified for, as will be discussed in greater detail later, the distance from the calcified mitral ring to the apex of the heart in the frontal view is a measurement of the length of the posterior wall of the left ventricle. This measurement may be useful in deciding whether aortic insufficiency or mitral stenosis is the predominating lesion in a patient who has both, because the ventricular hypertrophy of aortic insufficiency tends to cause the posterior wall to be elongated, while mitral stenosis tends to shorten it.

The most striking instance of posterior wall shortening in the present series is shown in Fig. 7. This heart was obtained from a 30-year-old housewife who, with a history of childhood rheumatic fever, had relatively mild congestive heart failure until two weeks before death. The presence of marked mitral insufficiency in addition to mitral stenosis and a giant left atrium were recognized clinically. At autopsy, the left atrium had a capacity of 800 c.c. The mitral valve was a rigid shelf-like structure across the mitral ring with the anterior and posterior leaflets failing to meet, leaving a defect of 1.0 cm. in its broadast diameter. There was no right ventricular dilatation and the free wall of the right ventricle was normal in weight. The left ventricle and septum weighed 130 grams which is also in the normal range.

In the illustration the ventricular heart of this case is compared with a normal heart with the same apex-to-aortic valve length. A diagram of the normal heart is added to assist in orientation. In the upper photographs the diaphragmatic surfaces of the two hearts are shown, and in the lower photographs the hearts have been opened in the transverse plane to show the left ventricular inflow and outflow tracts. It can be seen that in the heart with mitral stenosis the inflow tract of the left ventricle is remarkably shorter than the outflow tract, while the two are of relatively the same length in the normal heart. The mitral ring is markedly tilted so that, no longer perpendicular to the direction of the inflow tract, it is now oblique to it. Thus, the circumference and the antero-posterior diameter of the mitral ring are greatly increased in the heart with mitral stenosis. This has, of course, been described before in mitral stenosis but has usually been attributed to dilatation of the left ventricle with stretching of the ring. In this instance, it is due to shortening of the posterior wall of the left ventricle, for no significant left ventricular dilatation was present.

What is the mechanism of this remarkable shortening of the posterior wall of the left ventricle? It is not due to a simple reorientation of the walls of the ventricle with a region of the posterior wall becoming converted into apex because, if this were the case, the origins of the papillary muscles would be shifted toward the anterior wall. In this heart, the papillary muscles originate at about the normal distance from the apex of the heart on the posterior wall.[17] Nor can it be due to elongation of the anterior wall with the posterior wall remaining normal because the membranous portion of the septum, which represents one of the sites of attachment of the muscle of the anterior wall, was not distorted or increased in area; also, such stretching of the anterior wall would have been accompanied by hypertrophy of this region which was not seen either grossly or microscopically.

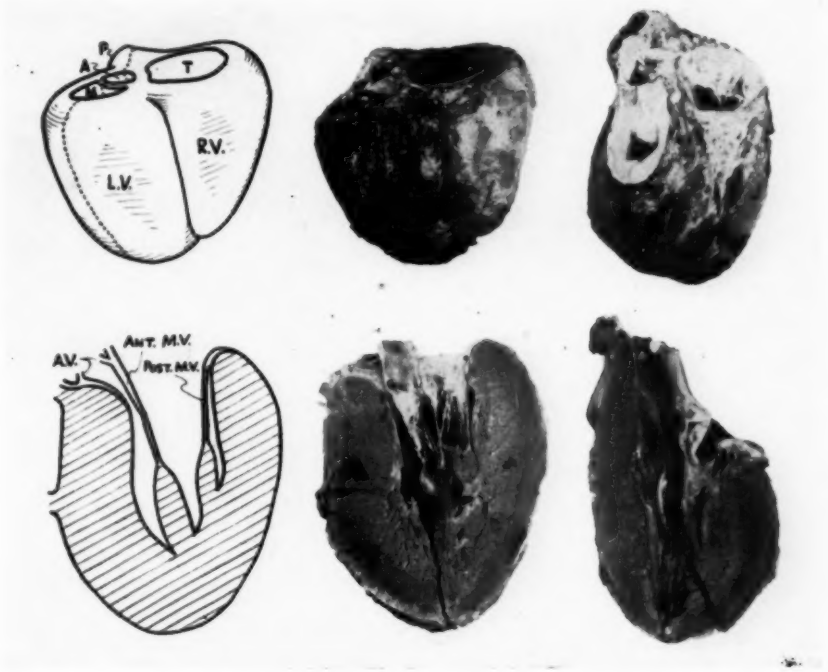

Fig. 7.—The ventricular heart in a case of mitral stenosis compared with the ventricular heart of a normal person, with diagrams for identifying the structures of the normal heart. In the upper photographs, the heart is viewed from its diaphragmatic or inferior aspect; in the lower photographs, the inflow and outflow tracts of the left ventricle are shown. The dotted line in the upper diagram indicates the line of incision that was made to expose inflow and outflow tracts of the left ventricle. *P*, pulmonary orifice; *A*, aortic orifice; *T*, tricuspid orifice; *M*, mitral orifice; *Ant MV*, anterior or aortic leaflet of the mitral valve; *Post MV*, posterior leaflet of the mitral valve; *AV*, cusps of the aortic valve.

It must be concluded that the shortening was due to selective atrophy of the portion of the ventricular muscle which is inserted into the posterior rim of the mitral-aortic ring. That atrophy (or hypertrophy) can take place in isolated regions or components of the myocardial syncytium has been recognized before.[20-23] It was not possible to identify the particular muscle bundle or bundles involved in this atrophy. However, attempts in this and other laboratories to

"unroll" the human heart, as has been done with hearts of other mammals, have been unsuccessful, for true cleavage planes are extremely difficult to demonstrate in the human heart.[9,18,19]

When heart muscle undergoes atrophy, the muscle fiber diminishes to a certain critical diameter beyond which dissolution and resorption take place.[24] Histologic examination of the posterior wall of this heart showed a marked variation in fiber diameter, but there was no obvious decrease in average diameter as compared with myocardium from other regions of the left ventricle. It is presumed that much of the myocardium of this region had gone on to dissolution and resorption.

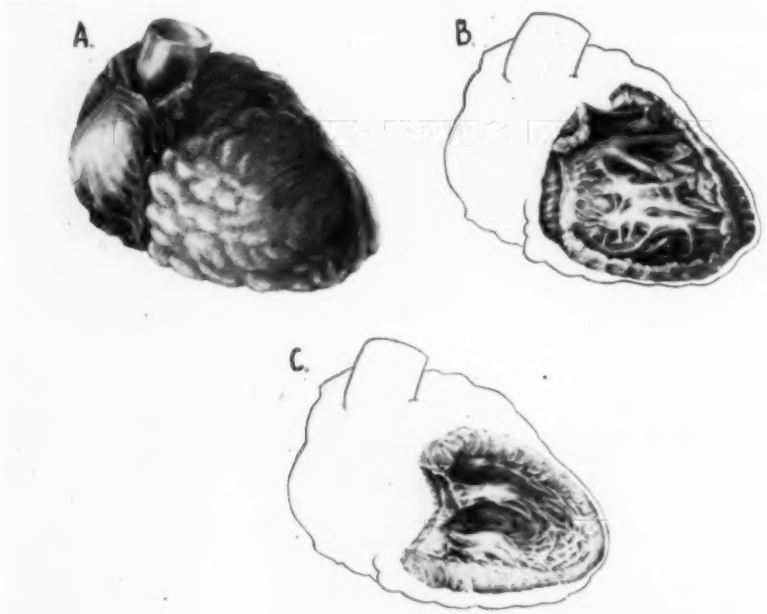

Fig. 8.—The heart with mitral stenosis at three stages of dissection viewed frontally as it lies in the body. *A*, the intact heart; *B*, the ventricular heart with the free wall of the right ventricle removed; *C*, cross section of the left ventricle exposing the inflow tract. Drawn to the same scale as the normal heart in Figure 4, illustrating the shortening of the posterior wall of the left ventricle, and the "double apex."

The likeliest explanation for the selective atrophy of the posterior wall of the heart in mitral stenosis is that the thickening of the valve leaflets and fibrosis of the chordae tendinae convert the valve into a rigid cylinder of dense scar tissue, immobilizing the posterior wall of the left ventricle with atrophy of this immobilized muscle. That immobilization of muscle leads to atrophy is well recognized for skeletal muscle. A cardiac parallel is seen, perhaps, in the myocardial atrophy which has been demonstrated in constrictive pericarditis.[25,26]

In order to understand the way in which mitral stenosis immobilizes the posterior wall of the heart, it is necessary to understand the sequence of changes

which take place in the mitral valve with the development of mitral stenosis, illustrated in Fig. 9. The first change which takes place in the anterior leaflet is a thickening of the more membranous and delicate posterior edge of the leaflet, producing a ledgelike structure on the atrial surface of the leaflet. This thickening is due to fibrous tissue deposition which gradually spreads onto the line of insertion of the chordae tendinae, producing the characteristic broadening of the insertions of the chordae. It then extends as a plastic, adhesive process down the chordae, thickening and fusing them, until finally they are enveloped in a dense inflexible layer of fibrous tissue and are only recognizable as radiating ridges on the ventricular surface of the fibrous sheath.

It can be seen that the "shortening" of the chordae tendinae, which has long been thought to be a characteristic feature of mitral stenosis, is more apparent than real. This was demonstrated in the present study by measuring the entire length of the anterior mitral valve, from the aortic cusps to the papillary muscles. In the eleven hearts with severe mitral stenosis in which this measurement was made it proved to be normal. Rokitansky recognized that there was no real shortening of the chordae in mitral stenosis, and Magarey has recently added additional evidence to this effect.[27]

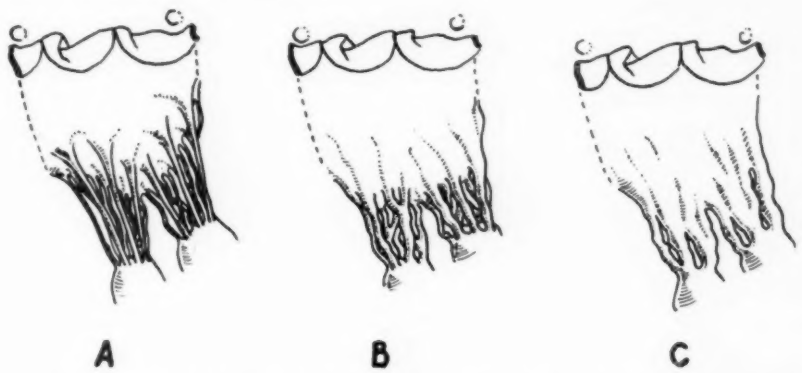

Fig. 9.—The sequence of changes in the anterior (aortic) leaflet of the mitral valve during the development of mitral stenosis. The cusps of the aortic valve, the orifices of the right and left coronary arteries, and the papillary muscles are shown. Note that while the chordae tendinae appear to become shorter, the valve itself is unchanged in length.

Thus, in mitral stenosis, the anterior mitral valve becomes converted into a dense rigid sheath of fibrous tissue, incorporating the chordae tendinae and extending to the tips of the papillary muscles. This process apparently often develops more rapidly in the anterior leaflet of the mitral valve than in the posterior leaflet. However, there is considerable variation in the rate and extent of the process in different regions of the same valve. Generally, the lateral region of the mitral valve, where the anterior and posterior leaflets meet, is slower to become involved in this process, and that is perhaps why the stenosed valve often has a slitlike or cruciate opening. Whether the stenosed valve becomes funnel-shaped or, more rarely, is a ledgelike structure, as in the present case, probably depends upon the rate at which the valves become involved and how rapidly the posterior wall undergoes atrophy.

There are probably several different factors which may play a part in the production of mitral insufficiency in the course of mitral stenosis. However, in the present case, the atrophy of the posterior wall was the most important one. The fibrous envelopment of the anterior valve had produced a leaflet which was longer than normal and had considerably more surface area than the normal leaflet. Nevertheless, the retreat of the posterior wall was so marked that even this greatly extended anterior leaflet could no longer cover the mitral orifice and mitral insufficiency resulted. Doubtless the marked degree of mitral insufficiency in this case accounted for the giant left atrium, a sequence of events which has been recognized before.[28]

It is commonly believed that mitral insufficiency leads to left ventricular hypertrophy. Although this may often be the case, in this heart the left ventricular weight was in the low normal range. Furthermore, there was no evidence of right ventricular hypertrophy or dilatation, which are often considered to be the first ventricular effect of mitral stenosis. That the right ventricle is somehow "protected" and that the patient may have remarkably little disability up to the terminal illness has been previously recognized as characteristic of the giant left atrium syndrome.[29-31] However, its explanation is unknown.

It is currently believed that marked mitral insufficiency is a contraindication to mitral valvulotomy in the surgical treatment of mitral stenosis. However, in certain cases where the insufficiency is due to atrophy of the posterior wall rather than solely to intrinsic valve deformity, might not valvulotomy release the immobilized wall and improve myocardial function? Only increasing skill on the part of the cardiac surgeon and more critical study of patients will answer this. It is unlikely that any of the resorbed muscle would regenerate, but perhaps the valvulotomy would release the remaining ventricular muscle to compensatory hypertrophy.

The role of ventricular muscle atrophy in mitral stenosis is of interest to the cardiac surgeon and internist in another regard. When valvulotomy was first conceived as a feasible therapeutic measure for mitral stenosis, it was expected that, after successful release of the stenosed valve, the patient would rapidly return toward normal, for the only difficulty was thought to be the obstruction to flow through the mitral valve. However, this proved to be not usually the case. Although often the patient shows some improvement immediately after operation, maximal improvement is usually not reached for many months following successful valvulotomy. The reason for this must be related to the status of the myocardium, for the effects on heart muscle of immobilization by the rigid valve of mitral stenosis are probably quite analogous to the effects on skeletal muscle of prolonged immobilization in an orthopedic cast. The muscle undergoes atrophy and loss of strength, coordination, and efficiency and, when the cast is finally removed, many months of graduated exercise and retraining are necessary before the muscle is restored to normal function. Apparently the myocardium undergoes a similar loss of substance, strength, and efficiency in mitral stenosis, not only because of the internal "cast" due to the rigid valve but also because of the chronic reduction in cardiac output. Releasing the immobilized mitral valve can produce improved heart function only when the heart

muscle has itself regained its anatomic and physiologic capacities, and this may well take as long for cardiac muscle as for skeletal muscle.

Another interesting feature of this case is the extent to which the aortic valve was deformed by the alteration in left ventricular structure. There was no evidence of aortic valve disease at autopsy, but, as can be seen in the photograph, the plane of the aortic valve was markedly tilted out of its normal relationship to the direction of the outflow tract. Although the aorta in this region was normal in diameter, the aortic ring was greater than normal in circumference because of its oblique position in the aorta. There was no basal diastolic murmur in the present case, and the arterial pulse pressure was normal. However, it is conceivable that in certain cases this architectural deformity of the aortic ring might produce functional aortic insufficiency.[32]

LEFT VENTRICULAR HYPERTROPHY AND DILATATION

The most conspicuous change in the architecture of the left ventricle in left ventricular hypertrophy is the circumferentially symmetric thickening of the wall of the ventricle, with the septum participating equally with other regions in this increase in thickness, as shown in Fig. 3, *C*. Although this change might seem self-evident, it has not always been thought so simple, and in earlier two-dimensional studies of hypertrophy there was considerable controversy whether the septum hypertrophied as much as the free wall of the left ventricle. Three-dimensional dissections leave little doubt, however, that the septum undergoes essentially parallel changes with the rest of the left ventricle in left ventricular hypertrophy.

In addition the chamber elongates, giving the ventricle a more narrowly parabolic shape which from a physical point of view is perhaps a more effective contour for realizing maximum work for a given degree of wall contraction.[33] Generally, the increase in wall thickness is symmetric along the length of the chamber as well as over its circumference ("concentric hypertrophy"). However, as the hypertrophy becomes more marked or when it becomes complicated by dilatation as in congestive heart failure, the apical segment of the chamber dilates and the wall of this region becomes thinner than the wall at the base ("eccentric hypertrophy"). This may be an elemental hydrodynamic consequence of the greatly increased intraventricular pressures, converting the inflow-outflow tract pattern from a narrow V-shape to a U-shape in much the same way as high velocities and flow pressures tend to straighten a hose or other conduit. Such eccentric hypertrophy appears earlier in the course of hypertrophy of aortic insufficiency than in hypertrophy of aortic stenosis or hypertension. This earlier dilatation in aortic insufficiency seems also to influence both the degree and the histologic features of the hypertrophy, for the heart is not usually as heavy and the connective tissue proliferation in the myocardium is considerably greater in aortic insufficiency than in either aortic stenosis or hypertension.[34,35]

Regarding the lengthening of the walls in hypertrophy, Kirch suggested that usually the outflow tract of the ventricle elongates first, and only when the hypertrophy is marked does the inflow tract become equally elongated.[36] This

observation has been widely accepted. However, in twenty-four hearts with left ventricular hypertrophy in the present series, this has not been confirmed. The reasons for the difference in findings are (1) Kirch's tabulated data do not support his conclusions in many instances, and (2) he did not actually measure the lengths of the inflow and outflow walls of the heart, but rather the superior and posterior walls, which are parts of the inflow tract only. This occurred because he used a two-dimensional method of dissection and "lost" the inflow and outflow tracts. He made two longitudinal incisions in the wall of the left ventricle, one anterior and the other posterior to the papillary muscle of the free wall, removing a sector of about 45 degrees from the total circumference of the ventricle. He then flattened the heart, and made his measurements along the margins of these two incisions. These are not measurements of opposite walls of the ventricle but of its superior and posterior walls.

The dissections in the present series of cases suggest that the way in which the walls lengthen is determined less by the lie of inflow and outflow tracts than it is by the asymmetric anatomy of the chamber. Thus, the portion of the ventricle which rests on the diaphragm is prevented by the immobility of this structure from bowing, and this surface of the heart remains flat. Then, the anterior region of the left ventricle is embraced by the outflow tract of the right ventricle which, in turn, is contained by the anterior angulation of the aorta. These structures appear to inhibit changes in the contour of the anterior wall of the left ventricle. On the other hand, the posterior and superior walls of the left ventricular are unrestrained and show the most marked changes in coutour, becoming bowed and elongated beyond the mitral ring. These aspects are illustrated in Figs. 10 and 11.

The elongation of the free wall of the left ventricle probably is due principally to a reorientation of the myocardial fiber layers of this region. The fibers of one myocardial layer slip into a more interior layer, reducing the radial number of muscle fiber layers. However, each layer now contains more fibers so that the wall itself is lengthened more than it is thickened. Such consolidation of fibers into fewer radial layers has been shown to take place with ventricular dilation where the ventricular walls are often greatly elongated and thinned, but where there may be no reduction in the total number of fibers and sometimes even an increase in individual fiber diameter.[40] In hypertrophy, thinning of the elongated walls is usually not apparent, perhaps because there is often a marked increase in connective tissue accounting for a considerable portion of the increased weight of the ventricle.[36,38]

There is another anatomic feature which determines the way in which the left ventricle is altered in hypertrophy. Normally the portion of the left ventricle bordering the mitral ring bulges outward from the chamber while the portion bordering the aortic ring bulges into the chamber. With hypertrophy this difference becomes exaggerated, the convexity of the mitral portion becoming a conspicuous bulge beyond the margin of the mitral ring, while the inward bulge of the aortic region deeply invades the outflow tract, producing a true conus aorticum of the left ventricle.[38,39] This is shown in Fig. 12.

That the bulge into the outflow tract may sometimes actually compromise flow in this region was demonstrated in one heart in the present series. In this heart, which showed considerable left ventricular hypertrophy due to aortic stenosis, a small endocardial pocket was seen on the wall of the left ventricle at the region of maximal thickening of the conus aorticum. Unlike the endocardial pockets which are commonly seen in aortic regurgitation and face the aortic outlet, this pocket faced the apex of the heart. This means that during systole there must have been extremely high velocity and considerable turbulence of flow in this region of the outflow tract (Fig. 13). Such an endocardial pocket in left ventricular hypertrophy has been described only once previously.[40]

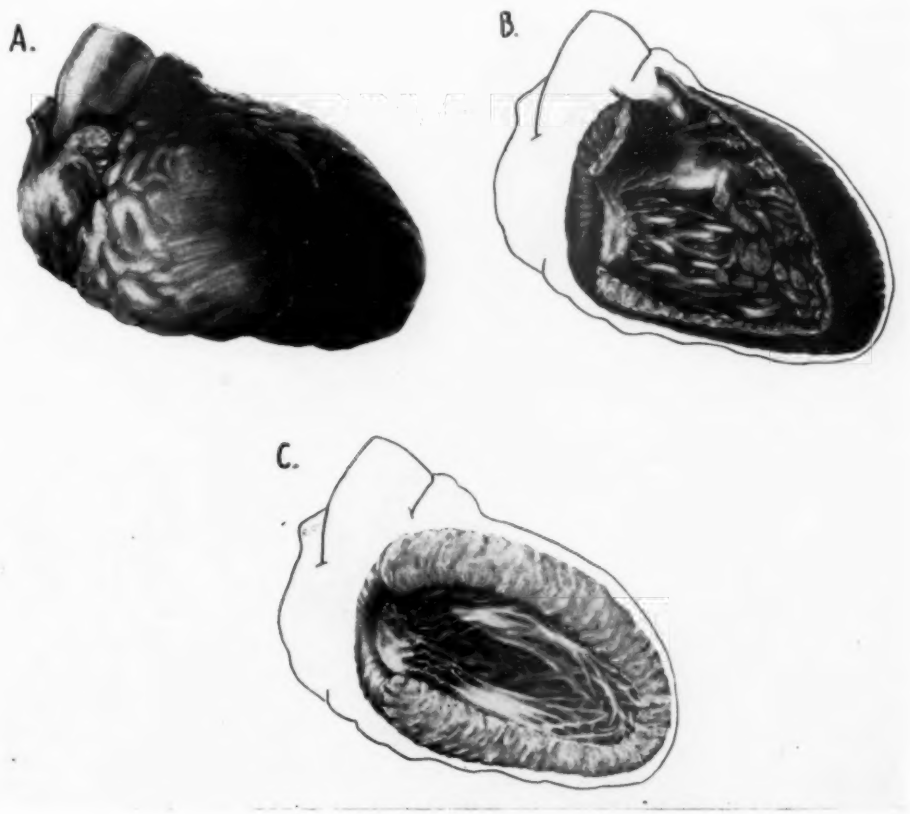

Fig. 10.—The heart with left ventricular hypertrophy at three stages of dissection viewed frontally as it lies in the body. *A*, the intact heart; *B*, the ventricular heart with the free wall of the right ventricle removed; *C*, cross section of the left ventricle showing the inflow tract. Drawn to the same scale as Figs. 4 and 8, illustrating the increase in the area of the septum and the elongation of the posterior and superior walls of the left ventricle.

The effects of hypertrophy on the mitral portion of the left ventricle are shown in Fig. 11 where a normal and a hypertrophied left ventricle-and-septum are shown. In the upper figure it will be noted that the diameter of the mitral-aortic ring is the same in the two ventricles, illustrating the rigidity of the skeleton

of the heart in the presence of marked muscle alterations. In the lower figure the relatively greater elongation of the posterior wall than of the anterior (septal) wall is shown, the ventricular myocardium extending considerably beyond the mitral ring in this region.

The elongation of the posterior and superior walls causes the plane of the mitral valve to become tilted so that it lies more nearly parallel with the plane of the aortic valve, as shown in Fig. 12. It will be noted in this figure that in left ventricular hypertrophy the mitral ring is tilted in an opposite direction to its tilt in mitral stenosis. This difference can occasionally be seen fluoroscopically when the mitral ring is calcified. (Calcification of the mitral ring may be seen under many circumstances and is not restricted to rheumatic valvular disease.)

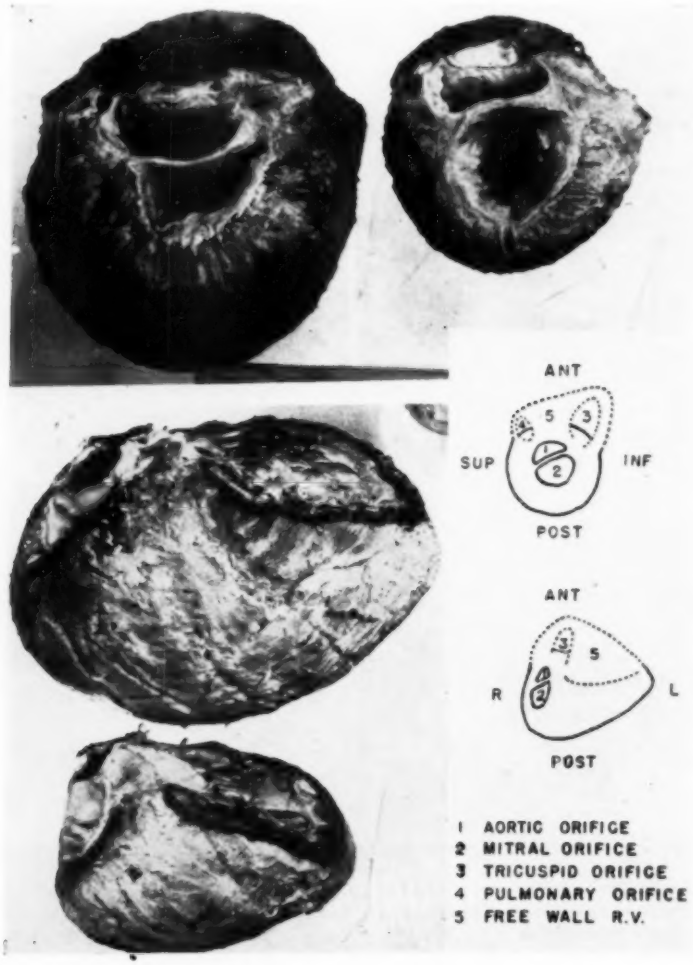

Fig. 11.—Two views comparing the normal and the hypertrophied left ventricle. The diagrams indicate the positions of the hearts for each view. The same hearts were used for each photograph. Note the elongation and bowing of the posterior and superior walls of the hypertrophied left ventricle with consequent tilting of the mitral ring. The septal wall is also elongated but shows no change in contour. The line of dissection of the free wall of the right ventricle was marked with indelible ink before photography. From Grant, R. P.: Circulation **7**:899, 1953 (Fig. 7), Grune & Stratton, Inc.

The calcification of the mitral ring involves only the portion of the ring where left ventricular muscle is inserted and, therefore, is confined to the posterior rim of the ring.[41] It is seen as a crescentic opacity fluoroscopically, and in the antero-posterior view will be concave rightward or leftward depending upon the tilt of the plane of the ring. When mitral stenosis is marked the calcific mitral ring will be concave rightward, that is, J-shaped; when left ventricular hypertrophy is marked it will often be concave leftward, that is, C- or L-shaped. (Although occasionally calcification of the mitral ring is described as circular rather than crescentic this can only happen when there is also calcification of the aortic cusps, for the mitral ring has no ligament anteriorly, only the broad surface formed by the anterior leaflet of the mitral valve and the root of the aorta.)

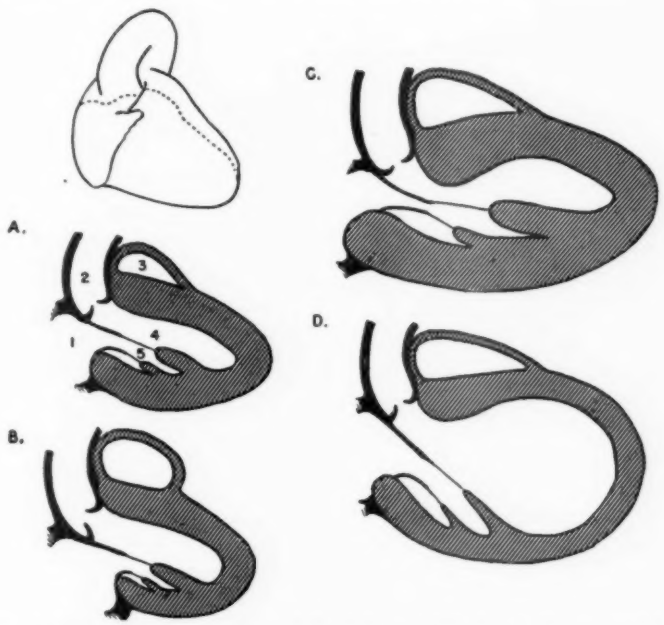

Fig. 12.—The inflow and outflow tracts of the left ventricle in, *A*, the normal heart; *B*, mitral stenosis; *C*, left ventricular hypertrophy; *D*, left ventricular dilatation. The diagram in the upper left corner shows the heart viewed frontally as it lies in the body, and the dotted line indicates the plane of incision to cut across the inflow and outflow tracts of the left ventricle. *1*, left atrium; *2*, aorta; *3*, conus or outflow tract of the right ventricle; *4*, outflow tract of the left ventricle; *5*, inflow tract of the left ventricle.

An architectural abnormality of left ventricular hypertrophy which has become a clinical syndrome is that described by Bernheim forty years ago. The Bernheim syndrome consists of marked left ventricular hypertrophy or dilatation where the hypertrophied septum bulges into the outflow tract of the right ventricle and obstructs it, producing the clinical picture of right ventricular failure (edema, ascites, elevated venous pressure with no signs or symptoms of pulmonary congestion). Whatever the clinical merits of this syndrome, pathologically it has many shortcomings, because the method used to "prove" it is inadequate and the pathologic findings which have been reported can be explained more satisfactorily otherwise.

The method used by Bernheim and most subsequent writers for demonstrating the obstruction of right ventricular outflow has been to make a single section of the heart, cutting transversely across the left ventricle.[42,43] However, as can be seen in Fig. 1, the outflow tract of the right ventricle is at right angles to the long axis of the left ventricle, and such an incision runs parallel with the outflow tract of the right ventricle rather than across it. Furthermore, in all

Fig. 13.—Endocardial pocket facing the apex in a heart with left ventricular hypertrophy due to aortic stenosis. The convexity of this region of the left ventricular wall (the conus of the left ventricle) can be seen where the wall was cut adjacent to the pocket. The cusps of the aortic valve are deformed and the chordae tendinae of the anterior leaflet of the mitral valve are somewhat thickened.

reports of this syndrome where photographs of the sections are reproduced, the section must have passed through the middle or apical third of the left ventricle, for the papillary muscles of the left ventricle are shown in the section. But since the outflow tract of the right ventricle occupies the medial region of the right ventricular chamber, it overlies the basal third of the left ventricle and, as was described earlier, is even more basal in the presence of left ventricular hypertrophy. Accordingly, it can be concluded that the method for dissection used in the reported cases of the Bernheim syndrome did not expose the principal route of the outflow tract of the right ventricle. In addition, the septum has a slight

outward convexity in all hearts, normal and abnormal. This is the normal contour of the left ventricle in this region, as shown in Fig. 2 and does not mean the septum is bulging into the right ventricle. Finally, it is well to remember that the right ventricle is capable of marked and rapid dilatation when its outflow is obstructed.[44] If the septum ever tended to obstruct right ventricular outflow, the free wall of the right ventricle would rapidly dilate, nullifying the obstruction. In short, the published evidence on the Bernheim syndrome does not adequately demonstrate that such a syndrome exists pathologically. In the present series of cases, no instances of significant obstruction of the right ventricular outflow tract by left ventricular hypertrophy were encountered.

To turn next to left ventricular dilatation, whether or not accompanied by hypertrophy, the most striking architectural change is the eccentric distribution of the dilatation. The portion of the left ventricular chamber which lies in front of the anterior mitral valve is much more dilated than is the portion behind this valve. Kirch described this as a greater dilatation of the outflow tract than of the inflow tract.[36] However, the anteromitral portion of the chamber includes the apical region of the chamber as well as the outflow tract. With dilatation, this apical segment also becomes dilated, causing the papillary muscles to appear to rise higher on the posterior wall of the heart than normally, as shown in Fig. 13.

The explanation for the eccentric distribution of the dilatation probably lies principally in the strategic position of the anterior mitral valve. It traverses the chamber and all alterations in the diameter of the left ventricular chamber—even the systolic and diastolic excursions of the heart—must accommodate to the presence of this structure. The dilating heart may be compared with inflating a balloon which has had a rubber band cemented to opposite walls. The physics of elasticity is such that with inflation the stress rises more slowly in the rubber band than it does in free parts of the wall of the balloon and, therefore, the rubber band restrains distention of the walls of its points of attachment. In the dilating heart the elastic band is the anterior mitral valve. However, it has an eccentric position in the chamber, extending from the mid-point of the mitral-aortic orifice to the apical third of the posterior wall. Accordingly, the restraining effect is applied to the posterior wall, especially the part which lies between the mitral ring and the origins of the papillary muscles.

There are probably other factors which play a part in this eccentric distribution of dilatation. The anterior mitral valve consists partly of muscle (papillary muscle) and partly of tendon (the chordae and the leaflet), and one might think that the lower elasticity of the tendon in the mitral valve would prevent dilatation of the posterior region of the heart. However, as will be seen, this reasoning may not apply to the particular circumstances under which dilatation occurs. Perhaps, also, the alterations in cardiac contour in the early stages of dilatation cause the various regions of the left ventricle to develop differences in magnitude of intramyocardial tension or differences in duration of the contracted state which damage the "tonus" and lead to greater dilatation of these regions.

The role of the papillary muscle in dilatation is of particular interest. Whatever the evolutionary reason for the appearance of papillary muscles as parts of

the anterior mitral valve[45], they serve an important function in providing a competent valve. The contraction of the papillary muscles shortens the valve so that during systole the mitral leaflet remains taut at all stages of cardiac contraction. This was recognized over a hundred years ago by Peacock and others who described cases of left ventricular dilatation where the papillary muscle had become "absorbed" into the dilating wall. During systole the mitral valve no longer shortened and instead ballooned into the left atrium producing mitral insufficiency as manifested by a loud apical systolic murmur.[46] This syndrome has not been recognized in recent times, perhaps partly because the diagnosis of mitral insufficiency in left ventricular disease has lost considerable prestige among clinicians in the intervening years.

When left ventricular dilatation is prolonged, the mitral valve is often elongated. Nearly always these hearts also show hypertrophy. However, the increase in ventricular weight is not as striking as is the increase in ventricular volume, and the papillary muscles, although wider than normal at their bases, are remarkably tapered, blending imperceptibly into chordae. On histologic section the papillary muscles show considerable replacement of muscle by connective tissue, perhaps histologically approximating the cases of "absorbed" papillary muscles described by Peacock. Three examples of this were encountered in the course of the present study, but clinical histories were not available in any of them.

The anterior mitral valve is also elongated in left ventricular hypertrophy, whether or not dilatation is present. The reason for this is that the ventricular chamber is elongated in hypertrophy as a consequence of the lengthening of the walls described earlier. And since the papillary muscles originate in the apical third of the posterior wall, the mitral valve also becomes elongated. The papillary muscles are blunt, thick structures, generally showing the same degree of hypertrophy as the ventricular wall.

However, the remarkable feature of the elongation of the anterior mitral valve in both hypertrophy and dilatation is that the three parts of the valve (the leaflet, the chordae, and the papillary muscles) participate equally in the elongation. This was unexpected because, with resting muscle more elastic (more easily stretched) than tendon, one would expect that elongation of the mitral valve would be mostly or even entirely due to stretching of the papillary muscle. However, in all cases where the mitral valve elongation was marked, the ratio of the length of the papillary muscle to the length of the leaflet and the chordae tendinae remained essentially normal. The explanation for this does not lie in some hormonal factor similar to that which leads to stretching of the pelvic ligaments in pregnancy, for the other parts of the cardiac skeleton did not show this stretching.

A more plausible explanation perhaps is that while resting muscle is more elastic than tendon, contracted muscle has elastic properties which are much closer to those of tendon.[47] This would certainly provide a satisfactory explanation for the mitral valve elongation in left ventricular hypertrophy due to hypertension, for the tension in the mitral valve during systole in these hearts would be considerably above normal and might well exceed the resistance to stretch of tendon.

But how can the elongation of the tendinous parts of the mitral valve be explained in cases of cardiac dilatation where there had apparently been no increase in intraventricular pressure? It was pointed out earlier that the posterior wall and papillary muscles do not undergo as marked stretching as the remainder of the ventricle in the course of left ventricular dilatation. Perhaps because of this they are able to produce greater than normal tensions during systole; indeed, this region may generate greater than normal tensions in order to compensate for a mechanical failure of the more dilated regions. If this were the case they might generate tensions which exceed the resistance to stretch of tendon. An even more intriguing possibility is that dilatation of the heart in this group of cases might be due to a disturbance of the tonus of cardiac muscle while it is in the contracted state—the tonus of contraction[48]—rather than a disturbance of its tonus in the relaxed or diastolic state which is the usual explanation for cardiac dilatation.

SUMMARY

With the advent of newer diagnostic and therapeutic techniques in cardiology it has become more and more important that the clinician understand the functioning or three-dimensional architecture of the heart and the changes in this architecture which take place with one or another form of heart disease. A method was devised for studying at autopsy the three-dimensional structure of the heart. Approximately sixty selected normal and abnormal hearts were studied by this method, and those findings which are of clinical interest are presented.

In the normal heart, the left ventricle has a relatively horizontal position in the body with its mitral and aortic orifices facing the right side of the body. The aorta makes a nearly 90 degree angle with the direction of the outflow tract of the left ventricle before it emerges from the pericardium. The right ventricle lies altogether anteriorly to the left ventricle; and the septum, which is parallel with the frontal plane of the body, is intrinsically a part of the left ventricle rather than an independent muscular partition between the two ventricles.

The sequences of change in the course of development of right ventricular hypertrophy and dilatation are described. An anatomic explanation for the nearly invariable occurrence of right ventricular hypertrophy whenever left ventricular hypertrophy is marked is offered.

An aspect of the pathology of mitral stenosis which has not been widely appreciated is the shortening of the posterior wall of the left ventricle. The implications of this shortening for the development of mitral insufficiency are discussed, and a striking example is presented in detail. The shortening of the posterior wall is believed to represent atrophy of this region of the left ventricle due to the immobilizing effect of the rigid mitral valve elements. It is pointed out that the shortening of the chordae tendinae of mitral stenosis is more apparent than real.

The architectural changes in left ventricular hypertrophy are described. It was found that the hypertrophy tends to be circumferentially symmetric, with the septum participating equally with other regions in the hypertrophy. When

the hypertrophy is marked the distal part of the outflow tract of the left ventricle is converted into a narrow conus aorticum, and evidence is offered that occasionally this narrowing may produce turbulence and obstruction to outflow from the left ventricle. The pathologic basis for the Bernheim syndrome is examined, and it is shown that the method of dissection used by Bernheim and his followers was inadequate for demonstrating obstruction of the right ventricular outflow tract. No instance of right ventricular outflow obstruction due to left ventricular hypertrophy was encountered among the hearts examined, and the existence of this syndrome is questioned. The three-dimensional changes which take place with left ventricular dilatation are described, and the role of elongation of the mitral valve elements in left ventricular hypertrophy and in dilatation is discussed.

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NONSPECIFIC MYOCARDITIS IN ACUTE RHEUMATIC FEVER*

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RHEUMATIC heart disease is one of the few conditions in which the physician diagnoses myocarditis. Aside from the clinical manifestations in such cases, he is well aware of the existence of the rheumatic nodules or Aschoff bodies in the myocardium and their association with rheumatic myocarditis. Yet Aschoff nodules, though frequently found in acute rheumatic disease, are isolated microscopic structures situated consistently within the interstitial tissue of the myocardium. Though it is conceivable that such interstitial nodules might give rise to changes in the conductivity of the specific muscle fibers if located in certain regions, it is difficult to understand how they can cause symptoms of myocarditis and how they can be responsible for fatal myocardial failure. In an attempt to answer these questions the myocardium of patients, with clinical evidence of myocarditis, who had died with acute rheumatic heart disease have been reexamined.

In the more recent literature few references pointing to diffuse myocarditis in instances of acute rheumatic fever are to be found. Sacks[1] advanced the view that diffuse cellular infiltration of the myocardium may represent an exaggeration of the less copious leukocytic collections which accompany Aschoff bodies. Skworzoff[2] found exudative inflammation of varying intensity in the myocardium, including inflammatory edema, lymphoid and histiocytic cells, and a few neutrophilic leukocytes. He also noted small foci of necrosis in the heart muscle. In his opinion, it is diffuse myocarditis rather than the rheumatic nodule that causes the clinical picture of myocarditis and unexpected death. He found that the diffuse form of myocarditis is more common in children and reported four such cases. Wright-Smith[3] believed that the myocardial insufficiency, often prominent in the acute phase, may be explained by a combination of inflammation, cloudy swelling, and ischemia resulting from coronary obstruction. While it is true that coronary arteritis is sometimes present in acute rheumatic fever, thrombotic occlusion is very rare. Griffith and Huntington[4] reported three patients with rheumatic fever whose abrupt deaths seemed to have been caused by acute anaphylactic coronary angiitis superimposed on low-grade rheumatic carditis. The microscopic sections of the myocardium showed a number of inflammatory changes in addition to Aschoff bodies. Zischinsky[5] very recently reported the cases of two children with rheumatic fever who died unexpectedly, one after an

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illness of only seven days. Autopsy disclosed no evidence of endocarditis, but rather a diffuse myocarditis. Aschoff bodies were present. There was no detailed description of the myocardial changes.

MATERIAL AND METHODS

Twenty-two cases, in which death was due to acute rheumatic heart disease and clinical evidence of myocarditis had also been recorded, were selected from eighty-six cases classed "rheumatic heart disease" in the files of the Armed Forces Institute of Pathology. The principal reason for the rejection of many of the cases was that severe valvular deformities had been caused by rheumatic fever, and the patient had died from myocardial failure with or without characteristic myocardial changes. Furthermore, since this study is limited in scope to recent rheumatic heart disease, only those cases with recent myocardial changes and typical Aschoff bodies were chosen.

CLINICAL DATA

The clinical records of the twenty-two patients were reviewed and pertinent data listed. The ages of the patients varied from 4 to 25 years, eight being either 18 or 19 years old. The duration of the final disease was from one week to seven months (one patient), with an average of approximately nine weeks. Some of the patients were admitted to the hospital because of what appeared to be acute rheumatic fever, with headache, pain in the back, knees and lower extremities, and fever. Shortness of breath, cough, and expectoration of bloody sputum were common. Tachycardia and gallop rhythm were present in seven patients. The temperature of one patient who had tachycardia and gallop rhythm was normal or slightly above normal. The temperatures of fifteen patients varied from 99° to 103° F. Cyanosis was a common manifestation. Five patients died unexpectedly.

The duration of the disease was as follows: one patient was apparently well when death occurred. There was no history of preceding illness. Three patients died within the first week of the disease, and three others within the first month. Fourteen died at between five weeks and five months, the majority having been sick three months or less. Only one patient died as much as seven months after the first symptoms of rheumatic fever had appeared. These data are presented to illustrate the rapid, downhill course in patients with diffuse myocardial involvement.

Electrocardiographic records had been obtained in twelve cases. In two there was only a single record, while in the others from two to twelve records had been taken over a period of two to five and one-half months. Electrocardiographic evidence of myocardial involvement was noted in all twelve cases. S-T-T changes of a nonspecific pattern were present in eleven, first degree atrioventricular block in seven cases, and second degree atrioventricular block in one case. Paroxysmal tachycardia was noted in two patients. The majority of the patients showed atrioventricular block and contour changes. The instability of the changes, as revealed in serial records, gave added significance to minor abnormalities. In some cases a diagnosis of acute myocarditis was entertained only in view of the changing records.

The clinical diagnosis of acute rheumatic fever was made on all the patients except the one who died unexpectedly before admission to a hospital.

A short clinical summary of one of these cases (Acc. 112394) follows:

The patient reported on sick call because of pain of one day's duration in the calves, starting two days after a mild sore throat. He had had no serious illnesses, no previous attacks of rheumatic fever, and no operations. While the patient was on the train, pain settled in both knees and ankles and he could hardly walk. His knees became swollen. He was removed from the train by ambulance to a general hospital.

Both knees were swollen, red and tender, and warm to palpation. Erythematous patches were present over both lower tibiae. The ankles were painful on motion. The left middle meta-

carpophalangeal joint was red and swollen. The heart was not enlarged; there were no thrills or murmurs; rhythm was regular and rate rapid. The tonsils showed evidence of chronic infection; eyes, ears, nose, lungs, abdomen, and reflexes were within normal limits.

Laboratory data: Total leukocyte counts ranged from 13,000 to 14,000; hemoglobin was normal. Urinalysis showed a trace of albumin, with a few white blood cells and occasional casts. Sedimentation index was 28 mm./hr. An electrocardiogram showed sinus tachycardia, prolonged P-R interval, and S-T-T changes indicative of acute pericarditis. Pneumonic consolidation of the lower two-thirds of the left lung was observed on roentgenographic examination.

The patient ran a persistent fever but had few complaints. Joint symptoms subsided on intravenous salicylate therapy and sulfonamides. Pulmonary signs developed and became progressively worse. He died four days after admission. Temperature varied from normal to 103°F. and terminally was 100°F. Pulse ranged from 100 to 130, and respiration from 30 to 50 per minute. Blood pressure was normal throughout, 120/80 to 112/60 mm. Hg.

SUMMARY OF PATHOLOGIC FEATURES

The gross changes observed at autopsy in the twenty-two patients may be summarized as follows: all hearts were enlarged. Acute verrucous endocarditis involved the mitral valve alone in four patients; the mitral and aortic valves in ten; the mitral, aortic and tricuspid valves in three; the mitral and tricuspid valves in two; the mitral, aortic and pulmonic valves in one; and all four valves in two patients. Older endocarditis was present in twelve of these twenty-two hearts. Pericarditis encountered in seventeen patients was organized in four and acute in thirteen. A moderate degree of passive hyperemia was noted in the visceral organs of nineteen patients, and in only one other was it very severe.

MICROSCOPIC CHANGES IN THE MYOCARDIUM

As stated before, Aschoff bodies were found in every heart. In addition to these, the following changes were encountered:

Interstitial Myocarditis.—Surrounding the smaller blood vessels was a moderate to intense infiltration of lymphocytes. In all cases lymphocytes extended throughout the interstitium over a considerable length. An occasional histiocyte was found among these cells, but nowhere were there any multinucleated cells. Sometimes these lymphocytes were adjacent to an Aschoff body, but most commonly they were seen in isolated areas. Neutrophilic leukocytes, independent of lymphocytes, were found richly infiltrating large microscopic areas but still confined within the interstitial tissue. There were no foci of necrosis or abscess formation. These inflammatory cells were also observed where there were no Aschoff bodies. In older cases, smaller or larger areas of fibrosis were usually located in perivascular regions.

Parenchymatous Changes.—In eighteen hearts changes in muscle fibers were noted. They varied from foci showing severe degenerative changes with loss of striations to areas of necrosis involving several muscle bundles. At the periphery of the latter were polymorphonuclear leukocytes, a few lymphocytes, and endothelial leukocytes, with an occasional Aschoff cell among these leukocytes.

The most interesting lesions were encountered within the parenchyma. They consisted of circumscribed minute foci of degenerated or necrotic muscle

Fig. 1.

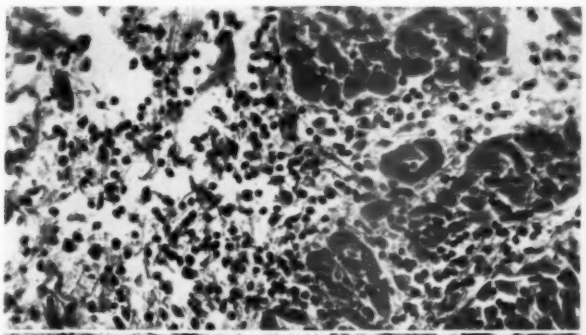
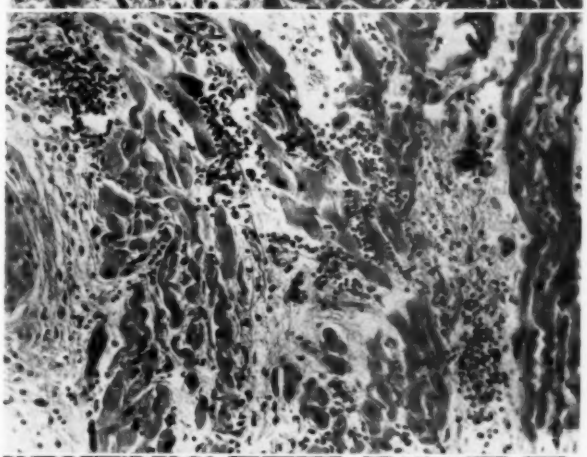


Fig. 2.



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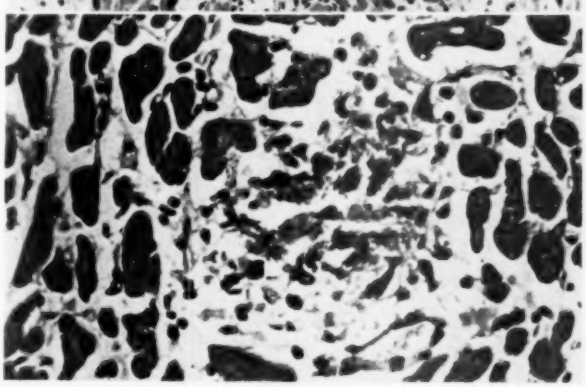

Fig. 1.—Intense lymphocytic infiltrations. Hematoxylin-eosin, X220. AFIP Acc. 185975.

Fig. 2.—Severe interstitial myocarditis. Fibrosis and replacement of muscle fibers by connective tissue. Hematoxylin-eosin, X116. AFIP Acc. 178786.

Fig. 3.—Early necrosis of muscles surrounded by inflammatory cells. Hematoxylin-eosin, X285. AFIP Acc. 198374.

fibers surrounded by small accumulations of endothelial leukocytes and lymphocytes, with an occasional mast cell, thus resembling granulomas. Multinucleated cells were also present, and Aschoff cells or Anitschkow's myocytes were often encountered. These formations, on superficial examination, simulated Aschoff bodies rather closely. However, they were not found in the interstitial tissue but involved muscle fibers, and invariably small areas of still recognizable but necrotic muscle fibers were found in their centers. Furthermore, the cells of this granuloma-like lesion were not arranged in parallel rows as the cells of an Aschoff body but surrounded the necrotic muscle fibers in irregular fashion. Nothing resembling microorganisms was seen in and adjacent to the necrotic region. In eight patients these accumulations were prominent, and in ten patients they were found after careful research.

Serous Inflammation.—In four instances the muscle fibers were spread apart by an edema-like material, suspended in which were a few lymphocytes, mast cells, and rare polymorphonuclear leukocytes. The adjacent muscle fibers showed degenerative changes.

Table I is included to show, side by side, pertinent myocardial changes and electrocardiographic alterations. It also tabulates the duration of the final illness, pertinent clinical notes, presence or absence of pericarditis, and the type of endocarditis.

DISCUSSION

In twenty-two instances of recent rheumatic fever, in addition to Aschoff bodies, a number of other changes were found in the myocardium. These were interstitial inflammations and changes within the muscle apparatus. The former consisted mainly of lymphocytic infiltrations, principally perivascular in distribution, independent in location from Aschoff bodies. These changes are similar to those often seen in the various nonspecific myocarditides and also in the myocardium in instances of subacute bacterial endocarditis.

More interesting, and probably of much greater significance, were changes in the muscle fibers themselves, consisting of the various forms of degeneration and minute foci of necrosis. The latter were sometimes pronounced and abundant. These foci were surrounded by inflammatory cells which caused them to appear as small granulomas, and at first glance they resembled Aschoff bodies. However, they were not seen in perivascular regions but in the muscle fibers, and the center of such foci was formed by definitely necrotic muscle fibers. The inflammatory cells at their periphery consisted mainly of endothelial leukocytes. Though Aschoff cells or Anitschkow's myocytes were identified, the arrangement of the cells was not that seen in the typical Aschoff body.

Because of the significance attached to Aschoff bodies and because of the evaluation of the lesions encountered within the myocardial fibers in this study, it was thought timely to again emphasize our criteria for Aschoff bodies.

It is, of course, realized that the Aschoff body, like any granuloma, is a perpetually changing morphologic entity. This has been clearly brought out by the various relevant opinions expressed during a pertinent discussion at the meeting

Fig. 4.

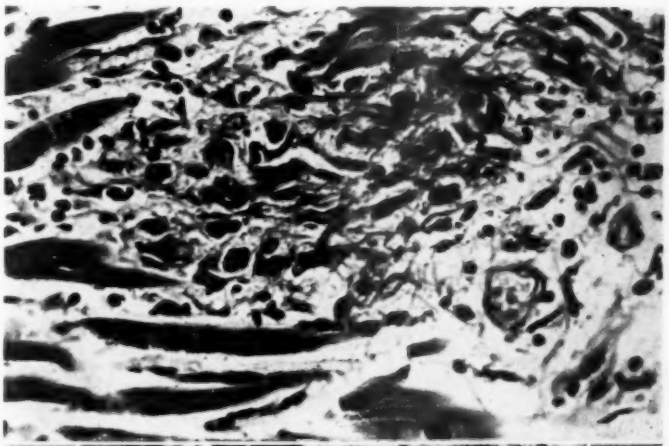

Fig. 5.

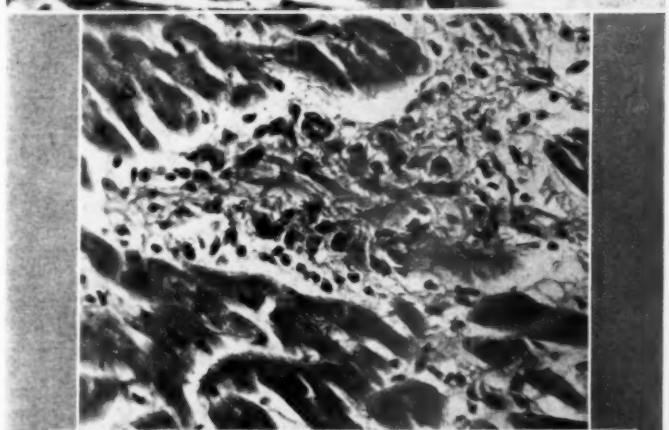

Fig. 6.

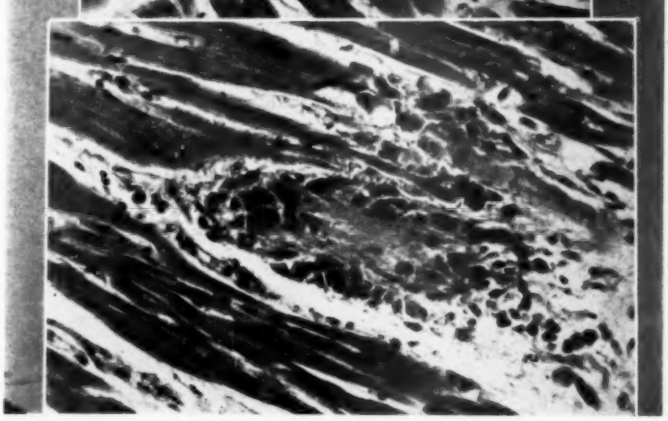

Fig. 4.—Granuloma with necrotic muscle fibers in center. Hematoxylin-eosin, X315. AFIP Acc. 198374.

Fig. 5.—Granuloma with necrotic muscle fibers in center. Muscle fibers are still clearly outlined. Hematoxylin-eosin, X250. AFIP Acc. 174747.

Fig. 6.—Well-developed granuloma. The muscle fibers in the center are barely recognizable. There are a few multinucleated cells at the periphery. Note absence of a perivascular distribution of this granuloma. Hematoxylin-eosin, X220. AFIP Acc. 174747.

TABLE I. CLINICOPATHOLOGIC FEATURES OF TWELVE CASES OF MYOCARDITIS IN RHEUMATIC FEVER WITH ELECTROCARDIOGRAPHIC RECORDS

CASES	DURATION OF FINAL ILLNESS	PERICARDITIS		CHANGES IN MYOCARDIUM		ENDOCARDITIS		EVIDENCE OF MYOCARDIAL FAILURE	CLINICAL NOTES	ELECTROCARDIOGRAPHIC CHANGES
		RECENT	OLD	INTERSTITIAL	PARENCHYMATOUS	RECENT	OLD			
I (185957)	6 days	+	−	+	++++	+	−	+	Pulmonary edema	Varying T-wave contour
II (198374)	7 wk.	+	−	+	++++	+	−	+	Marked dyspnea	1st degree atrioventricular block (P-R varies between 0.16 and 0.20 sec.)
III (205403)	3 mo.	−	+	+	++++	+	+	+	Pulmonary edema shortly after admission	Variations in S-T-T contour; second degree atrioventricular block (varies between 5:4 and almost complete)
IV (112394)	5 days	+	+	+	+	+	−	+	History attached	S-T-T indicative of acute pericarditis; first degree atrioventricular block (P-R varies between 0.18 and 0.24 sec.)
V (113168)	4½ mo.	+	−	+	++++	+	+	+	"Myocardial insufficiency even at bed rest"	Varying S-T-T contour; first degree atrioventricular block (P-R varies between 0.12 and 0.22 sec.)
VI (122067)	8 days	−	−	+	+	+	−	+	Severely dyspneic at admission	S-T depressions; atrioventricular dissociation, see Fig. 7
VII (129409)	2½ mo.	−	−	+	+	+	−	+		T-wave abnormalities; first degree atrioventricular block (P-R 0.20 sec.)
VIII (108852)	6 wk.	−	+	+	++++	+	+	+	Sudden development of pulmonary edema, sudden death	Supraventricular paroxysmal tachycardia
IX (109073)	?	+	+	+	++++	+	+	+	In extremis on admission, sudden death	First degree atrioventricular block (P-R 0.22 sec.)
X (109807)	5 wk.	−	−	+	+	+	+	+	Gallop rhythm, severely decompensated	Varying T-wave contour
XI (110277)	4 wk.	−	+	++++	+	+	+	+		Variations in S-T-T contour; first degree atrioventricular block (P-R varies between 0.16 and 0.20 sec.)
XII (120072)	7 wk.	−	−	+	+	+	−	+	Scarlet fever 4 wk. before onset, sudden death	T-wave abnormalities; first degree atrioventricular block (P-R varies between 0.19 and 0.24 sec.)

of the American Association of Pathologists and Bacteriologists in 1929,[6] the participants apparently discussing various stages in the development of the Aschoff body.

It has been emphasized before,[7] and it should be stated again, that while there are distinct variations correlated with the age of Aschoff bodies from the early fibrinoid swelling to scar formation, the only characteristic morphologically specific lesion is that described as the second stage[7] of the Aschoff body. The Aschoff body is always located in the interstitial tissue in the vicinity of a blood vessel. Necrotic foci or a fibrinoid material may still form the matrix of the body which consists principally of an accumulation of large cells showing one, and more rarely two or three, nuclei, which are often overlapping. These multinucleated cells may have ragged edges. The cytoplasm of these cells is basophilic, and the chromatin of the nuclei is either compact or arranged in the form of a "spider." The nucleus has also been described as owl-eyed[8] (myocardial reticulocyte, Aschoff cell, Anitshkow's myocyte, etc.). There are also a few lymphocytes and a very few histiocytes as seen in other granulomas. Also, a few polymorphonuclear leukocytes are found scattered at the periphery of the nodule. The larger cells, though there may be only a few, are arranged in parallel rows, sometimes only two or three such rows being recognized. Often, too, the cells are grouped in a palisading fashion. Perhaps depending upon the age of the cells or on the pressure of the surrounding tissue, the cells may be either compactly arranged, the Aschoff body presenting a somewhat elongated appearance, or the cells are well separated from one another by a fibrinoid material, the Aschoff body appearing rather square or round. As was stated before, it is fully realized that the observer may fail to recognize certain Aschoff bodies and thus fail to make a diagnosis of rheumatic myocarditis if such rigid criteria for identification are adhered to. On the other hand, he will be less likely to err if cellular infiltrations resembling Aschoff bodies, regardless of where in the heart they are located, are considered true Aschoff bodies. These strict criteria are of particular importance today in the evaluation of experimental work tending to reproduce rheumatic fever, since certain hyperergic reactions in the myocardium closely resemble Aschoff bodies.

It seems evident that the changes involving the muscle fibers themselves are of much greater importance in regard to the function of the heart than either Aschoff bodies, which are located in the interstitial tissues or the interstitial inflammation. It is interesting that among the twelve patients with these myocardial lesions whose electrocardiographic records were available (see Table), pulmonary edema, pronounced dyspnea, "myocardial insufficiency even at bed rest" or severe myocardial failure were stressed in the histories of seven patients and that two other patients had died unexpectedly. Three patients had been sick for eight days or less. One was brought to the hospital in extremis with no history of illness. Rapidly developing changes in the myocardial muscle fibers might well account for this clinical picture.

The cause of these foci of necrosis in the myocardium is obscure. If it is true that rheumatic fever is only the hyperergic reaction to nonspecific hemolytic streptococci, then these foci should be classed among hyperergic reactions. However, while lesions of panarteritic type are often present in the heart of hyperergic

animals, none were seen in our cases. It is also unlikely that the changes described can be attributed to chemotherapeutics or antibiotics since some of these patients died too quickly to receive any specific treatment. If it should be proved in the future that rheumatic fever is induced by a streptococcal infection, such a nonspecific myocarditis could be explained by the localization of organisms within the myocardium. While there are numerous reports on the isolation of streptococci from the circulating blood and from the heart valve, there are practically no systematic studies on cultures of the myocardium. Only Thomson and Innes[9] may be mentioned, in that they were able to grow hemolytic streptococci from the myocardium in one of their ten cases of acute rheumatic fever. If rheumatic fever is caused by an unknown agent, these lesions may constitute necrotic foci brought about by the toxic product of such an agent with a resulting tissue reaction, or they may be the result of a secondary infection. Whatever their origin may be, these lesions are probably responsible for the rapidly developing myocardial failure in some of the patients with acute rheumatic fever.

Murphy,[10] in a recent study of the myocardium of several young patients who died from acute rheumatic fever, concluded that very frequently early Aschoff bodies evolve from necrosis of bundles of muscle fibers. He found not only destructive lesions in the cardiac muscle fibers, but also evidence of an attempt at myofiber regeneration. Because the earliest changes leading eventually to the formation of Aschoff bodies were found within the muscle fibers, these lesions were designated as "myofiber Aschoff bodies." Murphy was also able to produce similar changes within the muscle fibers in a few of the rabbits which he injected with group A streptococci of different serologic types.

The main reasons for not classifying these granuloma-like lesions as Aschoff bodies are that they are not located in the interstitial tissue and are not perivascular. Aschoff[11] himself described rheumatic nodules as ". . . quite peculiar submiliary nodules within the interstitial tissue." Aschoff also mentioned the occasional finding of "parenchymatous . . . interstitial foci in addition to the specific rheumatic nodules, foci which very rarely assume significant proportions." In the absence of a more detailed description we cannot judge whether Aschoff had reference to the parenchymatous lesions we have described, though it seems likely.

The changes which Murphy described are apparently identical with those Aschoff mentioned and those described in this study. However, in our opinion, these muscular lesions are not Aschoff bodies since they are at variance with the criteria as to what constitutes a typical Aschoff body. While it is possible, as Murphy showed, that such lesions in the myocardium involving muscle fibers can be reproduced experimentally, a typical Aschoff body as yet has not been reduplicated in an experimental animal. The importance of classifying structures as Aschoff bodies, only if they fulfill the criteria, cannot be overstressed.

If these criteria as to what constitutes a specific rheumatic nodule or an Aschoff body were relaxed to include parenchymatous nodules with centers of necrotic muscle surrounded by cells like those usually found in an Aschoff body, then, of course, the lesions described here could be designated as Aschoff bodies. If such a broadened criterion were accepted, the morphologic diagnosis of rheumatic myocarditis would lose its specificity, for the only pathognomonic feature the morphologist now has for diagnosis would have been sacrificed.

Unfortunately, electrocardiographic records were available in only twelve of the twenty-two patients; some of these records were not taken seriatim and some are incomplete by current standards since they date back to a time when only the three classical limb leads were used. Furthermore, in trying to evaluate the significance of the alterations, we have to consider that some of the changes may not have resulted from the terminal illness, but may reflect pre-existing heart disease or the effects of medication, notably of digitalis. However, both the fleeting nature of some electrocardiographic alterations and the progressive nature of others, on the one hand, and the lack of typical digitalis contour on the other, suggest a causal relationship to the terminal episode of acute rheumatic fever. The presence of unstable abnormalities of the S-T-T complex in every instance where more than one record was available, of some form of auriculo-ventricular block in more than half of the cases, and the abnormal irritability

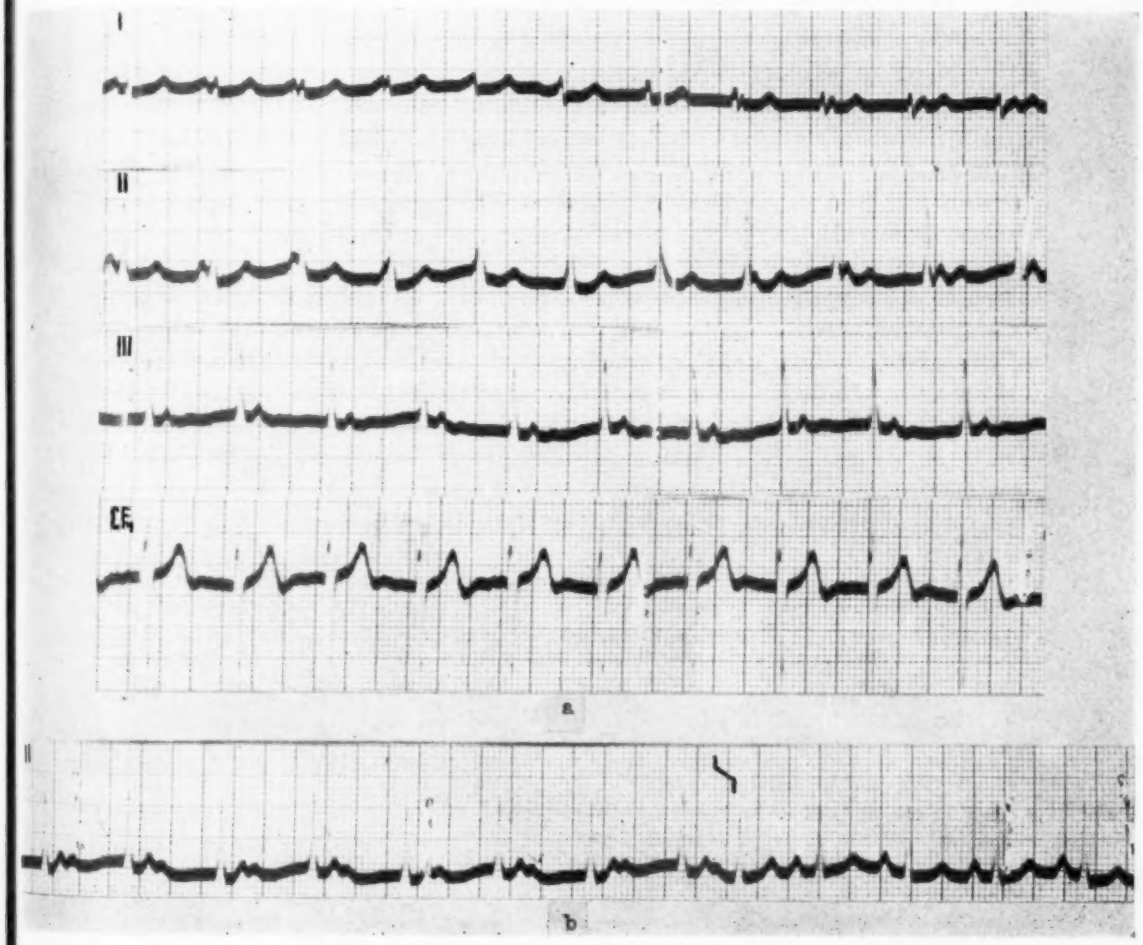

Fig. 7.—Electrocardiogram Case 6. Atrioventricular dissociation without atrioventricular block, a condition commonly seen in acute rheumatic myocarditis. Record (*a*) shows a regular rate of the ventricles (103 per min.) which is faster than that of the auricles (96 per min.). Complete dissociation between auricles and ventricles is present as a result of an abnormal irritability of the secondary pacemaker (atrioventricular node). In record (*b*) the same disturbance continues until a "premature" ventricular complex appears; the latter represents a ventricular "capture" and is followed by four more sinus beats with a normal P-R interval (0.16 sec.). AFIP Acc. 122067.

of the atrioventricular nodal pacemaker in two cases would suggest that these alterations are the result of a diffuse involvement of the myocardium. Therefore, it would appear warranted to ascribe the disturbances of conduction and formation of the cardiac impulse to the widespread nonspecific inflammatory process involving also the specific conduction fibers, rather than to the presence of isolated, strategically located Aschoff bodies. Because of the limited material available for study, we cannot state with certainty whether or not the presence of Aschoff bodies within the conduction system might be responsible for alterations of the electrocardiogram. It might be mentioned, however, that Gross and Fried[12] found Aschoff bodies in the bundle of His in only two of their sixty cases of active rheumatic fever. Thus, from the foregoing, we conclude in a preliminary fashion, that the electrocardiographic changes in acute rheumatic fever may be due primarily to the nonspecific myocarditis.

SUMMARY

This study deals with electrocardiographic changes and histologic findings in the myocardium of patients with rheumatic fever who had died from myocardial failure. Only cases with typical recent Aschoff bodies in the myocardium in the absence of severe valvular deformities were chosen. The majority of the patients had been sick three months or less. Shortness of breath, cyanosis, cough, expectoration of bloody sputum, tachycardia, and gallop rhythm were common. Electrocardiographic evidence of myocardial involvement was noted in all cases where electrocardiographic records were available. In addition to Aschoff bodies, interstitial nonspecific myocarditis was present in every instance. In eighteen of twenty-two hearts, the parenchymatous changes noted were characterized by circumscribed foci of necrotic muscle fibers surrounded by small accumulations of endothelial leukocytes, lymphocytes, with a few multinucleated cells and Anitschkow's myocytes. These granulomas resembled Aschoff bodies but varied in some essentials from true Aschoff bodies. It is suggested that the electrocardiographic changes in acute rheumatic fever are due to the nonspecific myocarditis.

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SINOAURICULAR NODAL DEPRESSION AND ATRIOVENTRICULAR NODAL RHYTHM DUE TO QUINIDINE

Report of a Proved Case

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ALTHOUGH the value of quinidine in the management of various cardiac arrhythmias is well recognized, there is little precise information on its serious untoward effects in man. In patients receiving the drug, a number of cardiac disturbances have been described. The etiologic role of the administered quinidine, however, usually could not be established because of the possible influence of other factors.[1]

Cessation of sinoauricular control of the heart beat with immediate development of atrioventricular nodal rhythm was observed repeatedly during the treatment with quinidine of premature ventricular beats and short paroxysms of ventricular tachycardia following an acute myocardial infarction in a 50-year-old man. The observations established definitely that the quinidine was the cause of this potentially serious cardiac effect.

CASE REPORT

M. S. (No. M 27591), a 50-year-old printer, entered the Beth Israel Hospital on Feb. 3, 1952, because of severe chest pain of several hours in duration. Two years previously he had had a posterior myocardial infarction treated at another hospital. Six weeks before admission he began to have mild exertional dyspnea and recurrent attacks of angina pectoris precipitated by exertion and relieved by nitroglycerine.

On the day of admission he developed severe anterior chest pain radiating down the right arm, not relieved by several injections of narcotics. He was admitted to the hospital two and one-half hours after the onset of the pain. At this time he was apprehensive, slightly cyanotic, and in mild respiratory distress. His respiratory rate was 25 per minute, rectal temperature was 98°F, blood pressure was 130/80 mm. Hg, and heart rate was 96 beats per minute with a regular rhythm interrupted by frequent premature beats. The mucous membrane of the nose and pharynx was somewhat reddened, and the tonsils were covered with follicular exudate. Examination of his chest showed dullness at both lung bases and coarse moist inspiratory râles over the lower one-third of the right posterior chest. The left border of cardiac dullness was 10 cm. to the left of the midsternal line in the fifth intercostal space.

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An electrocardiogram on admission showed changes consistent with an acute myocardial infarction: elevated S-T segments in Leads I, aV_L and V_2 to V_5; depressed S-T segments in Leads II, III, aV_F and V_E; QS deflections in Leads V_{2R}, V_1 and V_2. Subsequent electrocardiograms gave further indication of myocardial damage: inverted T waves in Leads I, II, aV_L, V_E, and V_2 to V_6 on the eighteenth and later hospital days; an R wave in V_2 on the twenty-third and forty-fifth hospital days, the last tracing being two days before discharge. Transient left bundle branch block was observed on the third hospital day. Ventricular premature beats occurred with varying frequency and will be discussed in detail.

Confirmatory evidences of the acute myocardial infarction were obtained from laboratory examinations and clinical observations. The white blood cell count rose to 19,950 cells per c. mm. on the fourth hospital day. The corrected erythrocyte sedimentation rate[2] rose to 42 mm. per hour on the thirteenth hospital day. A transient pericardial friction rub was heard on the third hospital day at which time the rectal temperature rose to 102°F.

Other laboratory tests showed a hemoglobin of 15 Gm. per 100 c.c., a serum nonprotein nitrogen of 30 mg. per 100 c.c., and a normal urine. A sputum culture on the fourth hospital day showed a coagulase-positive *Staphylococcus aureus*. A fasting blood sugar of 152 mg. per 100 c.c. was found on the second hospital day. An oral glucose tolerance test, done on the forty-sixth hospital day after three days of a daily 300 Gm. carbohydrate diet, was indicative of diabetes mellitus.

During the first five days in the hospital the patient had repeated attacks of severe chest pain requiring frequent injections of Demerol and morphine and the administration of oxygen. Procaine penicillin intramuscularly and then chloramphenicol (Chloromycetin) by mouth were administered to control his upper respiratory infection.

On the third hospital day the patient developed frequent hemoptyses, a protodiastolic gallop rhythm, and clinical evidence of extensive bilateral pulmonary congestion. A chest roentgenogram at this time showed generalized cardiac enlargement and bilateral pulmonary congestion but no evidence of pulmonary infarction. There was no clinical evidence of peripheral thrombophlebitis. The salt intake was restricted; he was given one dose of a mercurial diuretic on the sixth hospital day, and by the tenth hospital day his lungs had cleared and the hemoptysis had stopped. No digitalis glycoside was given at any time. Dicumarol therapy was started on admission and continued until the forty-ninth hospital day, being omitted from the sixth to the tenth days because of the hemoptysis. The prothrombin concentration was maintained at our currently accepted therapeutic level: between 5 and 12 per cent of normal as measured by the method used in this hospital.[3] By the end of the second week of hospitalization the patient was asymptomatic.

Because frequent ventricular premature beats were observed on admission by physical and electrocardiographic examinations, the administration of 0.5 Gm. of procaine amide hydrochloride (Pronestyl) every six hours was started on the first hospital day. This dosage appeared to have no effect on the frequency of the premature beats and, accordingly, after thirty-six hours, it was increased to 1.0 Gm. every six hours. The premature beats then disappeared and had not been observed again by the ninth hospital day when the administration of procaine amide was stopped.

No further cardiac irregularity was noted during convalescence until the twentieth hospital day. At this time ventricular premature beats were again observed; they persisted, with varying frequency, until the discharge on the forty-seventh hospital day. These premature beats were occasionally multifocal in origin (see Figs. 1 to 4) and sometimes became frequent enough to produce bigeminal rhythm (Fig. 1) and short runs of ventricular tachycardia. The patient remained asymptomatic throughout this period except for one very short episode of palpitation probably associated with a paroxysm of ventricular tachycardia. Both procaine amide and quinidine sulfate were administered orally in varying doses (Chart I) in an attempt to control the ectopic ventricular beats. Diphenhydramine hydrochloride (Benadryl) was also given for forty-eight hours (Chart I) because of a transient pruritic erythematous rash on his neck and in the antecubital spaces. The cardiac effects of these drugs were carefully watched in numerous electrocardiograms. The frequency of the ventricular premature beats was not consistently altered. A striking electrocardiographic change was observed, however, in conjunction with each of three

periods of quinidine administration: disappearance of the activity of the sinoauricular node and the development of atrioventricular nodal rhythm. Our detailed observations in this patient during these twenty-seven days are presented.

OBSERVATIONS

Sixty-seven electrocardiographic observations were made in this patient during the period from the twentieth to the forty-seventh hospital day. These records, usually of Lead II alone, and generally of 7 to 20 seconds in duration, have been carefully analyzed. Chart I shows the hospital day and the dominant site of impulse formation of each tracing, as well as the drug schedules. The dominant site of impulse formation was determined as follows: the disappearance of P waves from their usual positions preceding each characteristic supraventricular QRS complex indicated cessation of sinoauricular nodal control of the heart beat. Observations described below indicated that the pacemaker shifted to an area in or about the atrioventricular node (slower cycle length, wider QRS complex, discharge of the pacemaker by the retrograde conduction of premature ventricular beats). The cycle length during sinoauricular rhythm was determined in

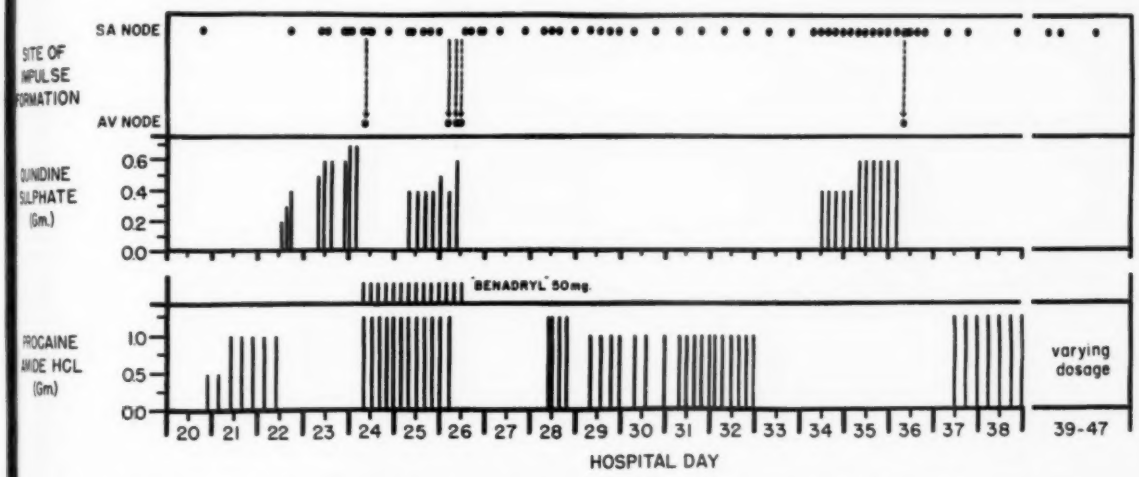

Chart I.—The relationship between drug administration and the changes in the site of impulse formation. (The procaine amide dosage during the final period varied: thirty-seventh to forty-first day, 1.25 Gm. every six hours; forty-second to forty-seventh day, three daytime doses of 1.0 Gm. each and a late evening dose of 1.25 Gm.)

several ways: the time between two sinoauricular beats not separated by an ectopic beat; one-half of the time between two sinoauricular beats separated by one premature ventricular beat; and one-third of the time between two sinoauricular beats separated by two premature ventricular beats. This was done because P waves could not be seen superimposed on the ectopic ventricular beats except in a few tracings (e.g., Fig. 4). During atrioventricular nodal rhythm the R-R interval gave a measure of the cycle length. P-R and QRS intervals were also determined. Other measurements will be indicated below. Accurate determination of the Q-T intervals was not possible because of the indistinct nature of the T waves.

The plasma quinidine concentrations reported were measured, in duplicate, by the fluorometric technique[4] after extraction of the drug from the plasma into ethylene dichloride and re-extraction into sulfuric acid.

Relation Between Quinidine Administration and the Development of Atrioventricular Nodal Rhythm.—With the exception of the five observations during quinidine administration, described here, the dominant cardiac rhythm was always (62 observations) of sinoauricular origin (Chart I). On each of three different days an absence of normal P waves was first observed approximately

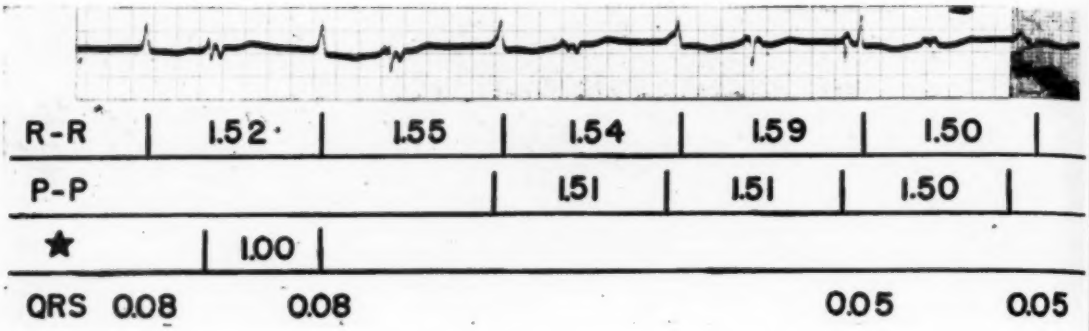

Fig. 1.—Twenty-fourth hospital day, 9:20 A.M. Lead II. In this and the other three figures all the measurements are to the nearest 0.01 second, and the intervals indicated by ★ are from a premature ventricular beat (or from the second premature beat of a pair) to the following supraventricular beat. The details of the various figures are discussed in the text.

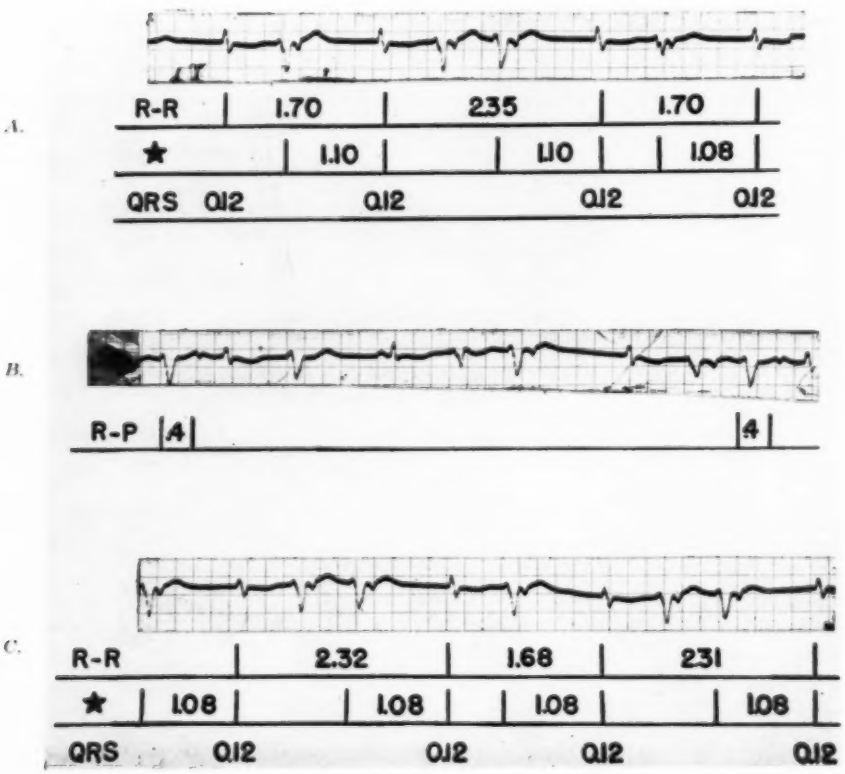

Fig. 2.—Twenty-sixth hospital day. *A*, 4:30 A.M.; *B*, 9:10 A.M.; *C*, 12 noon. Lead II.

four to five hours after a series of quinidine doses. On two of these three occasions, complete sinoauricular control was again observed within one hour. The observations were not sufficiently frequent to indicate more accurately the time of onset or the duration of the atrioventricular nodal rhythm.

Atrioventricular nodal rhythm was first observed on the twenty-fourth hospital day (Fig. 1) five hours and twenty minutes after the last dose of quinidine and one hour and five minutes after single doses of procaine amide and Benadryl. The electrocardiogram was taken at a moment of transition back to sinoauricular control. No P waves are seen in the first two supraventricular beats of this record. However, the next two such beats reveal both an atrioventricular and a slightly faster sinoauricular nodal pacemaker, the P waves becoming evident as increasing prominences on the ascending limbs of the R waves. The last two supraventricular beats have distinct P waves and are clearly of sinoauricular origin. No tracing had been taken during the preceding one hour and twenty minutes, and the initial change in the site of impulse formation may have occurred during that time. An electrocardiogram 55 minutes later again showed sinoauricular rhythm.

Absence of P waves in the beats of the dominant supraventricular rhythm was again observed in three separate electrocardiograms on the twenty-sixth hospital day in association with the administration of quinidine, procaine amide, and Benadryl (Fig. 2). The shift in pacemaker was first observed four hours and fifteen minutes after a dose of quinidine. Two more doses of this drug were given and the same electrocardiographic changes were again observed, three hours and twenty-five minutes and two hours and fifteen minutes, respectively, after the doses. One sinoauricular beat was present in these records (Fig. 2*B*). Four hours and fifteen minutes after the last dose, sinoauricular rhythm had returned, and it persisted in subsequent tracings.

Atrioventricular nodal rhythm was observed once more. It occurred on the thirty-sixth hospital day when quinidine alone was administered (Fig. 3). On this occasion, ten days after the last dose of Benadryl and four days after the last dose of procaine amide, a definite relationship between quinidine and the disappearance of sinoauricular activity was observed. Four hours and ten minutes after the last dose of quinidine, repeated shifts of the pacemaker between the sinoauricular and atrioventricular nodes were observed. The plasma quinidine concentration at this time was 3.9 mg. per liter. Forty minutes later complete sinoauricular control had returned. Subsequent plasma quinidine levels showed a gradual fall.

Rates of the Sinoauricular and Atrioventricular Rhythms.—Successive sinoauricular cycle lengths in any one record varied by no more than 0.03 second. In the numerous electrocardiograms these cycle lengths ranged from 1.05 to 0.68 second, corresponding to a heart rate of 57 to 88 beats per minute. The slowest rates (i.e., longest cycles) did not follow increasing doses of quinidine nor were they associated with the development of atrioventricular nodal rhyrhm. Sinoauricular cycle lengths, 0.75 (1.50/2: Fig. 1) and 0.84 to 0.86 (Fig. 3), in the tracings demonstrating the changing rhythm, were not the longest cycle lengths of their respective days. The slowest rates appeared to occur during a particular part of the twenty-four hour period: the hours from midnight to about 5 A.M. For example, the longest cycle lengths on the thirty-fifth and thirty-sixth hospital days, during the administration of quinidine, were observed at 4 A.M. and 4:30 A.M., respectively. Similarly, six days after the last dose of quinidine, on the forty-second hospital day, a cycle length of 1.03 seconds was observed at this same early morning hour (4:25 A.M.). It is apparent, then, that the development of atrioventricular nodal rhythm due to quinidine in this patient was not associated with gradual progressive slowing of the rate of impulse formation in the sinoauricular node.

The rate of the atrioventricular rhythm was slower than that of the closely-associated sinoauricular rhythm. Inasmuch as premature ventricular beats discharged the atrioventricular node, as will be seen below, the fundamental cycle length of the atrioventricular rhythm could be determined only when two atrioventricular nodal beats occurred which were not separated by an ectopic ventricular beat. This measurement was possible only in the electrocardiogram on the thirty-sixth hospital day (Fig. 3). At this time there were recorded several abrupt shifts back and forth between an atrioventricular rhythm with a cycle length of approximately 0.95 second (a rate of 63 beats per minute), and a faster sinoauricular rhythm with a cycle length of around 0.85 second (a rate of 71 beats per minute).

Auriculoventricular (P-R), Intraventricular (QRS), and Ventriculoauricular (R-P) Conduction.—Control P-R and QRS intervals before drug administration were normal: 0.16 second and up to 0.08 second, respectively. No change in the P-R interval was observed at any time during drug therapy. Prolongation of the QRS interval was observed only during atrioventricular nodal rhythm. On the first occasion (Fig. 1) the QRS intervals in the first two atrioventricular beats, although still within normal limits (0.08 second), are longer than in the last two sinoauricular beats in this tracing. It is likely that this apparent prolongation is due to concealed P waves in the longer QRS complexes. Certain beats in Fig. 3 (indicated by ●) differ from the others in that tracing and probably include concealed P waves of the returning sinoauricular pacemaker. This is clearly suggested by the prominence on the ascending limb of the R wave in the second of these beats in Fig. 3, *B*. The other atrioventricular beats in this figure are similar to those in Fig. 2. They have the same configuration and abnormally long QRS complexes. This delay in intraventricular conduction may have been due to a direct effect of quinidine or may have been associated with the change in the site of impulse formation. The latter explanation seems more likely inasmuch as supraventricular beats in the same tracing (Fig. 3, *B*) show normal or prolonged QRS complexes with sinoauricular or atrioventricular origin of the impulses, respectively. Furthermore, QRS prolongation was not observed at any other time during quinidine administration.

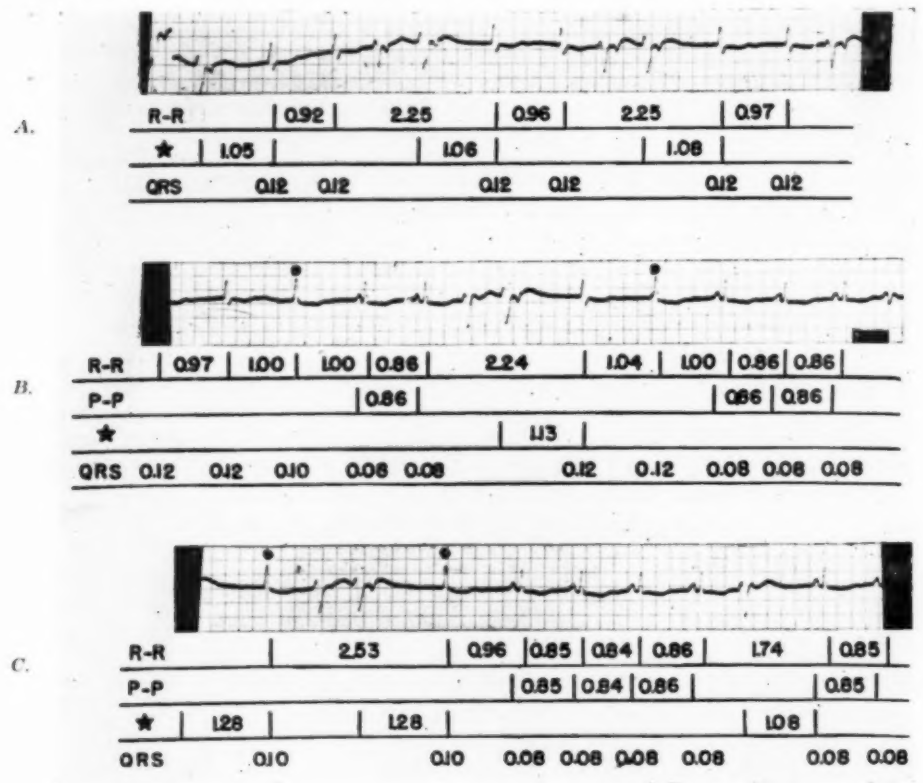

Fig. 3.—Thirty-sixth hospital day, 8:40 A.M. Lead II. *A*, *B*, and *C* are practically continuous. Beats marked ● are discussed in the text.

Retrograde conduction from the ventricle to the auricle, indicated by an inverted P wave following the ventricular complex, was apparent after 97 of 247 premature beats. The occurrence of this phenomenon was not related to the site of impulse formation or to drug administration. It was present during sinoauricular rhythm before any drugs were administered as well as during the atrioventricular rhythm associated with quinidine. The retrograde conduction time (R-P

interval) ranges up to 0.40 second and varies markedly even in successive premature beats of the same tracing. Only 11 of the 97 intervals exceeded 0.21 second. These long intervals all occurred during quinidine administration, three on the twenty-sixth hospital day when procaine amide and Benadryl were also being given, and eight on the thirty-sixth hospital day when quinidine alone was administered. Three of these intervals were over 0.30 second; each was closely followed by a supraventricular QRS complex suggesting that the very slow retrograde conduction permitted the retrograde impulse to re-enter the ventricle. The two longest R-P intervals were 0.4 second (Fig. 2, *B*) and were each followed by a P-R interval of 0.30 second: the other very long R-P was 0.31 second with a P-R of 0.19 second. At no other time was a grouping of beats observed that was suggestive of a coupling phenomenon.

Effect of Ectopic Ventricular Activity on the Sinoauricular and Atrioventricular Pacemakers.—Premature ventricular beats did not interfere with the rhythm of the sinoauricular node. The pauses after these beats were always sufficiently long to compensate for the prematurity of the beats. As clearly shown in Fig. 4, the P-P intervals which include one or two ectopic ventricular beats remain exact whole multiples of the single sinoauricular cycle length. The sinoauricular rhythm also remained undisturbed by a short run of ventricular tachycardia on the twenty-fourth hospital day.

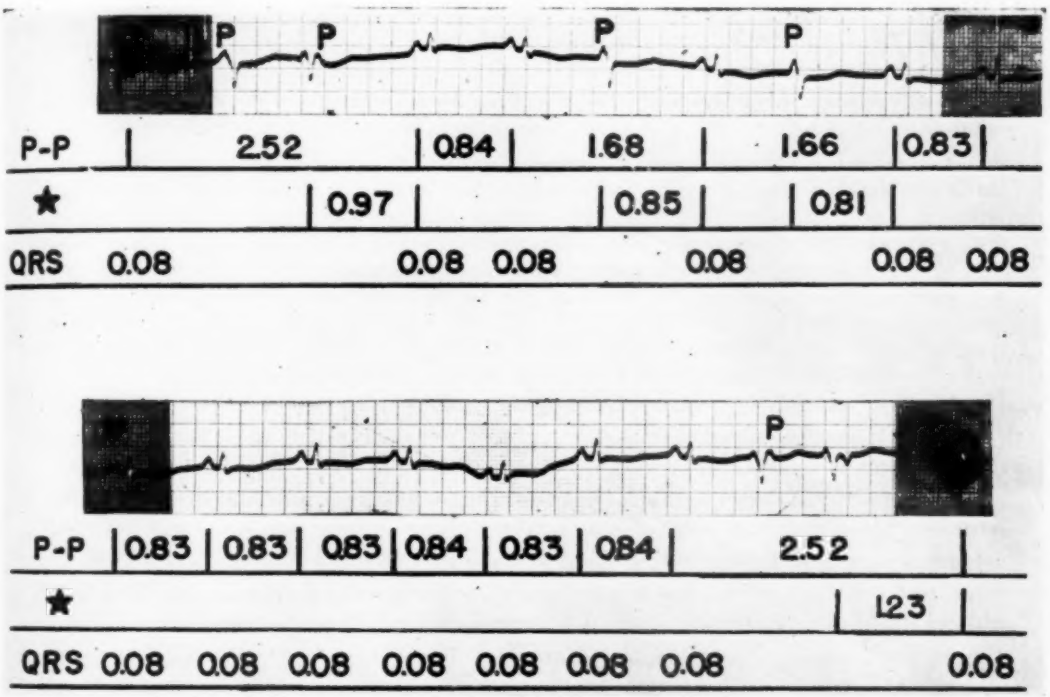

Fig. 4.—Twenty-fifth hospital day, 3:55 P.M. Lead II. The two strips are practically continuous. The P waves partially obscured by premature ventricular beats are marked by *P*.

When the dominant site of impulse formation changed, however, the rhythm of the new pacemaker in the atrioventricular node was markedly altered by the occurrence of premature ventricular beats. Retrograde conduction of these beats discharged the atrioventricular node. This is readily seen in the tracing on the thirty-sixth hospital day (Fig. 3, *A*). The single cycle length, between atrioventricular beats not separated by any premature ventricular beats, varies from 0.92 to 0.97 second. Where these atrioventricular beats are interrupted by a pair of ectopic ventricular beats, the R-R interval on two such occasions is the same: 2.25 seconds, not a whole multiple of the single atrioventricular cycle length. The interval from the second premature

beat to the subsequent atrioventricular beat, accordingly, is not compensatory but represents the time for retrograde conduction from the extrasystolic focus to the atrioventricular pacemaker (thus prematurely discharged) plus the first returning cycle of that pacemaker. The first three such intervals in the record show little variation (1.05, 1.06, 1.08) and are somewhat longer than the single cycle lengths.

The full effect of premature ventricular beats on the atrioventricular rhythm cannot be seen in Figs. 1 and 2, since the single cycle length cannot be measured. It is of interest, however, that on other days, the intervals, marked ★ on figures, from the premature ventricular beats (or from the second beat of a pair) to the subsequent atrioventricular beats (1.00 to 1.10) are very close to those noted above on the thirty-sixth hospital day (Fig. 3: 1.05 to 1.08). The corresponding interval during sinoauricular rhythm varied widely both on any one day (Fig. 4) and on different days. This suggests that the rate of impulse formation in the atrioventricular node was about the same on the three different days.

Effect of Drugs on the Ectopic Ventricular Activity.—Procaine amide and quinidine were administered to this patient in varying doses (Chart I), separately and together, in an attempt to control the premature ventricular beats and the short paroxysms of ventricular tachycardia. The frequency of the premature beats did not appear to be affected by these drugs or by the administration of Benadryl. Even at the times of atrioventricular rhythm associated with quinidine (Figs. 1 to 3) frequent ectopic ventricular beats persisted. They continued, as during sinoauricular rhythm and before drug administration, to arise from multiple ventricular foci, to show no fixed relationship to the preceding supraventricular beats, and to have the same slight degree of prematurity late in diastole.

No definite effect of drug administration on the occurrence of paroxysmal ventricular tachycardia was observed in this patient. On the twenty-third hospital day, twelve hours after the last preceding dose of quinidine, the patient had a sudden episode of palpitation and intense cyanosis lasting no more than a few minutes. No tracing was taken at this time. Subsequently, two short runs of ventricular tachycardia were recorded electrocardiographically: on the twenty-fourth hospital day during quinidine administration, and on the twenty-eighth hospital day after no drugs had been given for almost forty-eight hours. There was no further evidence of the occurrence of paroxysmal tachycardia during the last nineteen hospital days, although during several periods, once for as long as thirty-six hours, no drugs were administered.

DISCUSSION

Experimental observations both on the isolated heart and in the intact animal[5-10] indicate that one of the cardiac effects of quinidine is a depressing action on impulse formation in the sinoauricular node or on the spread of the impulse from that node. In dogs,[10] under sodium pentobarbital anesthesia, as plasma quinidine concentrations are progressively raised by continuous intravenous infusions of the drug, the following effects are observed. Sinoauricular slowing begins at low quinidine concentrations, progresses as the concentration is increased, and is accompanied by other electrocardiographic manifestations of interference with impulse formation in the sinoauricular node: sinus pauses and sinus arrhythmia not related to respiration. There is finally a disappearance of sinoauricular control of the heartbeat with transition to a slow atrioventricular nodal rhythm. Generally this transition is an immediate one, but asystole for as long as three to four seconds has been observed, in these experimental studies, following the cessation of sinoauricular control and before impulse formation has started in the atrioventricular node. The progression of the sinus slowing in the individual animal is closely related to changes in the plasma concentration of quinidine and the effect is rapidly reversible as the drug concentration is allowed

to decrease. The development of atrioventricular nodal rhythm, however, is an irreversible, preterminal effect in these experiments. Although drug infusion is stopped at this point, ventricular fibrillation and death always occur within a few minutes.

Although similar changes in the site of impulse formation have been observed in man in association with the administration of quinidine,[11-19] we have been unable to find any conclusive demonstration that the cardiac effects were due to the drug. To establish such a causal relationship in an individual case, it is essential that the cardiac effect be observed repeatedly in association with the administration of quinidine, and at no other time; that no other drug be given which might cause or contribute to the effect; and that the cardiac rhythm before quinidine administration should not be such as to be possibly associated with spontaneous depression of sinoauricular nodal activity. None of the reported cases satisfy all these requirements. Adequate control observations have generally been lacking, and only in one instance[12] has the reported phenomenon been observed more than once. In many cases digitalis has been administered with the quinidine; the relationship of digitalis glycosides to sinoauricular nodal depression is definite.[20] In every instance, the cardiac arrhythmia for which quinidine was given has been one which might have interfered with impulse formation in the sinoauricular node. These arrhythmias include: auricular fibrillation,[21] paroxysmal auricular tachycardia[22] and paroxysmal ventricular tachycardia.[23]

The observations reported here fulfill the requirements set forth and establish conclusively that quinidine was the cause of the repeated cardiac phenomena in this patient. On three separate occasions during quinidine administration there occurred an abrupt cessation of sinoauricular control of the heart beat and a resulting shift of the cardiac pacemaker to a secondary center of lower rhythmicity in the atrioventricular node. Numerous control observations, all showing sinoauricular rhythm, essentially eliminate the possibility that this was a spontaneous recurrent phenomenon not related to the drug. Procaine amide and Benadryl were being given in addition to quinidine at the time of the first and second episodes of atrioventricular rhythm. Each of these drugs has been found to have a quinidine-like effect on the heart.[24,25] No electrocardiographic changes were noted, however, when these drugs were given in the absence of quinidine. Furthermore, the administration of these drugs was stopped long enough before the third episode for any effects to have completely disappeared. At this time quinidine was the only cardio-active agent being given. Dicumarol, which was administered throughout most of the observation period has not been found to have any effect on the cardiac impulse-forming and conducting system in a large group of patients with acute myocardial infarctions.[26] Regular sinoauricular beats were present before and after the periods of atrioventricular rhythm. As has been shown, the frequent premature ventricular beats which occurred did not disturb the fundamental rhythm of impulse formation in the sinoauricular node.

The action of quinidine in this patient included a depression of the activity of the sinoauricular node, as shown by the analysis of the electrocardiograms.

The shift of control of the heart beat from this node to a site of slower rhythmicity in the atrioventricular node clearly indicates an interference with or depression of the faster pacemaker. Progressive sinoauricular slowing might have been expected as a precursor of a shift of pacemaker. However, the absence of such slowing does not preclude a depressing effect in or about the sinoauricular node.[27] No mechanism other than a direct effect of the drug could be found to explain this phenomenon. As already pointed out, the premature ventricular beats did not disturb the impulse formation in the normal pacemaker. The retrograde impulses following many of these premature beats were studied carefully in this connection, since it is known that such retrograde impulses to the atrium may discharge[28] and depress[22] the sinoauricular node. In this patient, however, during sinoauricular rhythm before drug administration, the ectopic beats were only slightly premature, occurring late in diastole, and accordingly, the retrograde impulses were always too late to discharge the sinoauricular node prematurely. During drug administration and atrioventricular rhythm the degree of prematurity of the ectopic beats remained slight; they continued to occur late in diastole. An increase in retrograde conduction time, previously described with quinidine,[29] was observed with some of the retrograde impulses. This effect could only have caused the atrial stimulation to occur even later in diastole, and thereby further decreased the likelihood of premature discharge of the sinoauricular pacemaker.

It was fortunate that, in this patient, the cessation of sinoauricular nodal activity was followed, at once, by the initiation of impulse formation in the atrioventricular node. Because of this immediate shift in the cardiac pacemaker, there were no abnormally long periods of asystole and the patient had no symptoms referable to the changes of rhythm. However, such interference with impulse formation may possibly lead to serious effects. If impulse formation is depressed in the atrioventricular node as well as in the sinoauricular node, a long period of asystole may readily occur. As mentioned, asystole for three to four seconds has been observed in animal studies, and even longer periods of complete cardiac standstill might result. Such a mechanism may be related to the instances of syncope[30,31] convulsions[30,31] and even sudden death[32-35] which have been observed in association with the administration of quinidine.

It is of interest that the doses of quinidine leading to the three episodes of altered rhythm were not excessive. The plasma quinidine concentration observed at the time of the third episode was only a moderate one: 3.9 mg. per liter. Larger doses have been used and much higher plasma levels (measured by the same technique) have been observed[1,36,37] without any untoward effects in many patients receiving quinidine. It seems likely, therefore, that the depressing effect of quinidine on sinoauricular impulse formation in this patient represented an unusual sensitivity of the sinoauricular node to the drug. Such sensitivity may have been related to the repeated episodes of myocardial damage: a recent anterior infarction and a posterior infarction two years previously. Interference with the blood supply to the sinoauricular node may have left this area more sensitive to drug effects. Similar localized variations in the cardiac sensitivity to reflex vagal stimulation have been described in patients with coronary artery disease.[38,39]

Careful electrocardiographic observations have been recommended as a safeguard during the administration of quinidine and of other potent drugs which act on the cardiac impulse-forming and conducting system. In the present case, however, except for the inconstant change in retrograde conduction, no effect of quinidine on the electrocardiogram could be detected close to the time of the abrupt change of pacemaker. Therefore, even with frequent observations, complete cessation of sinoauricular control of the heartbeat could not be avoided. However, when this phenomenon was observed, quinidine administration was stopped. Unlike the experimental results, the drug effect was rapidly reversible and normal sinus rhythm quickly returned. Continued administration of the drug might have led to further depression and more serious effects. Inasmuch as the patient was asymptomatic throughout the periods of changing pacemakers, and the differences in heart rates were not sufficient to permit clinical detection of the changes, the electrocardiograms were essential in limiting this toxic effect of quinidine.

It is of interest that the ectopic ventricular activity was not definitely affected by the use of three potentially effective drugs: quinidine,[40,41] procaine amide,[42] and Benadryl.[25]

SUMMARY

Conclusive proof is presented that cessation of sinoauricular control of the heartbeat with immediate development of atrioventricular nodal rhythm was due to quinidine, in a 50-year-old man with premature ventricular beats and short paroxysms of ventricular tachycardia following an acute myocardial infarction. This cardiac phenomenon was definitely related to the administration of quinidine on three separate occasions, although the doses were moderate and the plasma concentration was not high. The changes of pacemaker were abrupt and could not be foreseen despite frequent electrocardiograms. Although unassociated with symptoms in this patient, and quickly reversible when the drug was stopped, such an effect of quinidine is potentially serious.

It is a pleasure to acknowledge the assistance of the following: Dr. N. Geschwind, Dr. W. S. Karlen, and Dr. M. D. Schonfeld, the house officers, who helped care for the patient and who took many of the electrocardiograms; and Miss Lee Caplitz, who performed the quinidine analyses, and prepared the chart and figures.

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Clinical Reports

PROCAINE AMIDE OVERDOSAGE IN MYOCARDIAL INFARCTION

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OVERDOSAGE with oral procaine amide* has not, to our knowledge, been reported previously in myocardial infarction. It is the purpose of this case report to present such a patient, treated conservatively, with recovery.

CASE REPORT

J. B. H., a white man, aged 48 years, was admitted Nov. 2, 1952 to the University Hospital with an eighteen-hour history of nausea and vomiting, dyspnea, profuse sweating, and constricting substernal pain which radiated into the neck and down the medial aspect of both arms. Physical examination revealed blood pressure 110/80 mm. Hg, pulse 100, respirations 22, temperature 99° F. orally. The heart was not enlarged. Heart sounds were distant and occasional premature contractions were noted. No murmurs were heard. The remainder of the physical examination was negative. An electrocardiogram was obtained and revealed typical findings of an acute anterior myocardial infarction.

The patient was given initial doses of Dicumarol, and continuous intravenous heparin was administered for the first three days of hospitalization. The prothrombin time was thereafter maintained at about 40 seconds with daily doses of Dicumarol.

The premature contractions noted on admission were demonstrated by electrocardiogram to be ventricular in origin. The patient was then given procaine amide 0.5 Gm. orally every six hours with considerable reduction in number of premature beats. Physical signs remained much the same. The blood pressure varied from 94/70 to 110/80 mm. Hg. On Nov. 13, 1952 he was given 5.0 Gm. of procaine amide through error. One hour later he complained of numbness of his extremities, blurring of vision, nausea without vomiting, and dizziness. These symptoms subsided gradually over a period of about three hours after onset or four hours after the medication was administered. Blood pressure determinations during this period varied from 92/75 to 100/80 mm. Hg, and the pulse from 90 to 100. Fortunately, an electrocardiogram had been obtained about one and one-half hours before medication was given (Fig. 1). Serial tracings were taken throughout the next 24 hours (Fig. 2 and Fig. 3). Toxic effects demonstrable were: prolongation of QRS complex from 0.10 second to 0.14 second, Q-T prolongation from 0.44 second to 0.54 second, P-R prolongation from 0.18 to 0.20 second (Lead II), and alteration of the T wave in Leads II, III, AV_L, AV_F, and V_1 (Fig. 2). All these changes gradually returned to original levels within approximately eight hours. A tracing made the following day (Nov. 14) about 20 hours after medication (Fig. 3) shows no change over the tracing performed before procaine amide was administered.

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*Pronestyl, Squibb.

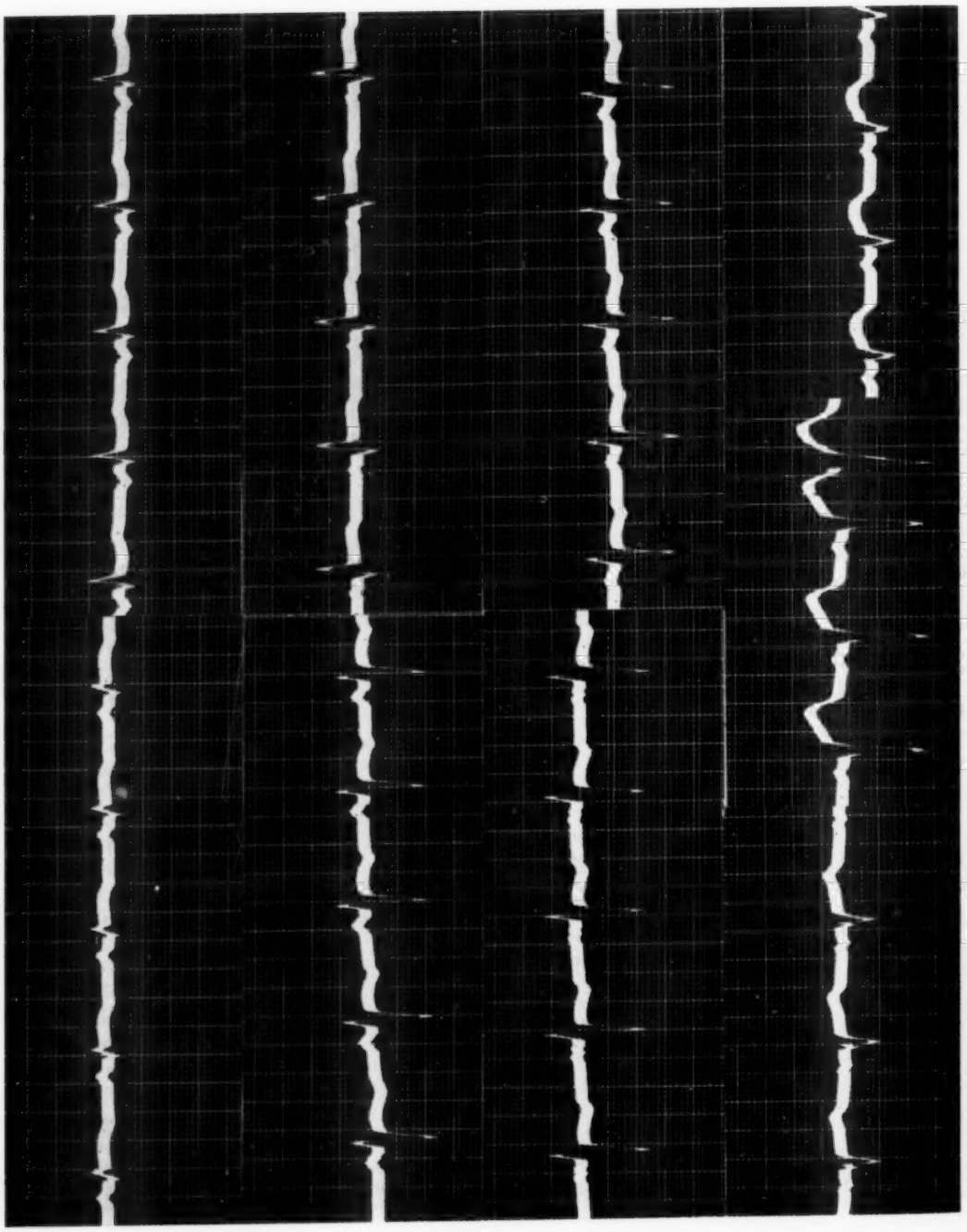

Fig. 1.—Electrocardiogram on J. B. H. performed one and one-half hours prior to administration of overdose of procaine amide. Findings characteristic of subacute anterior myocardial infarction.

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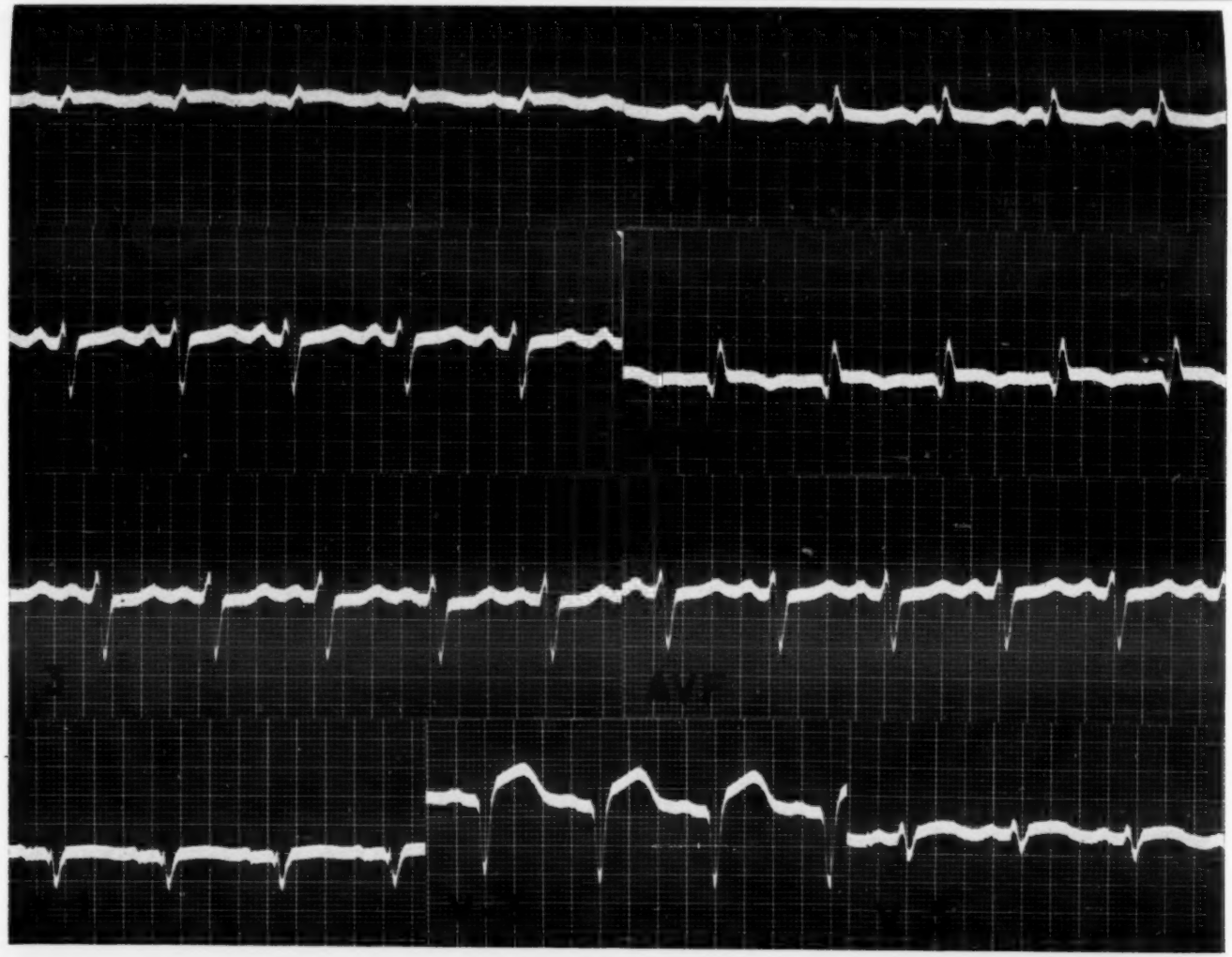

Fig. 2.—Electrocardiogram on J. B. H. approximately two hours after administration of overdose of procaine amide. Note P-R interval 0.20 second; QRS interval 0.14 second; and Q-T interval 0.54 second (Lead II) and changes in T waves in Leads II, III, AV_L, AV_F, and V_1.

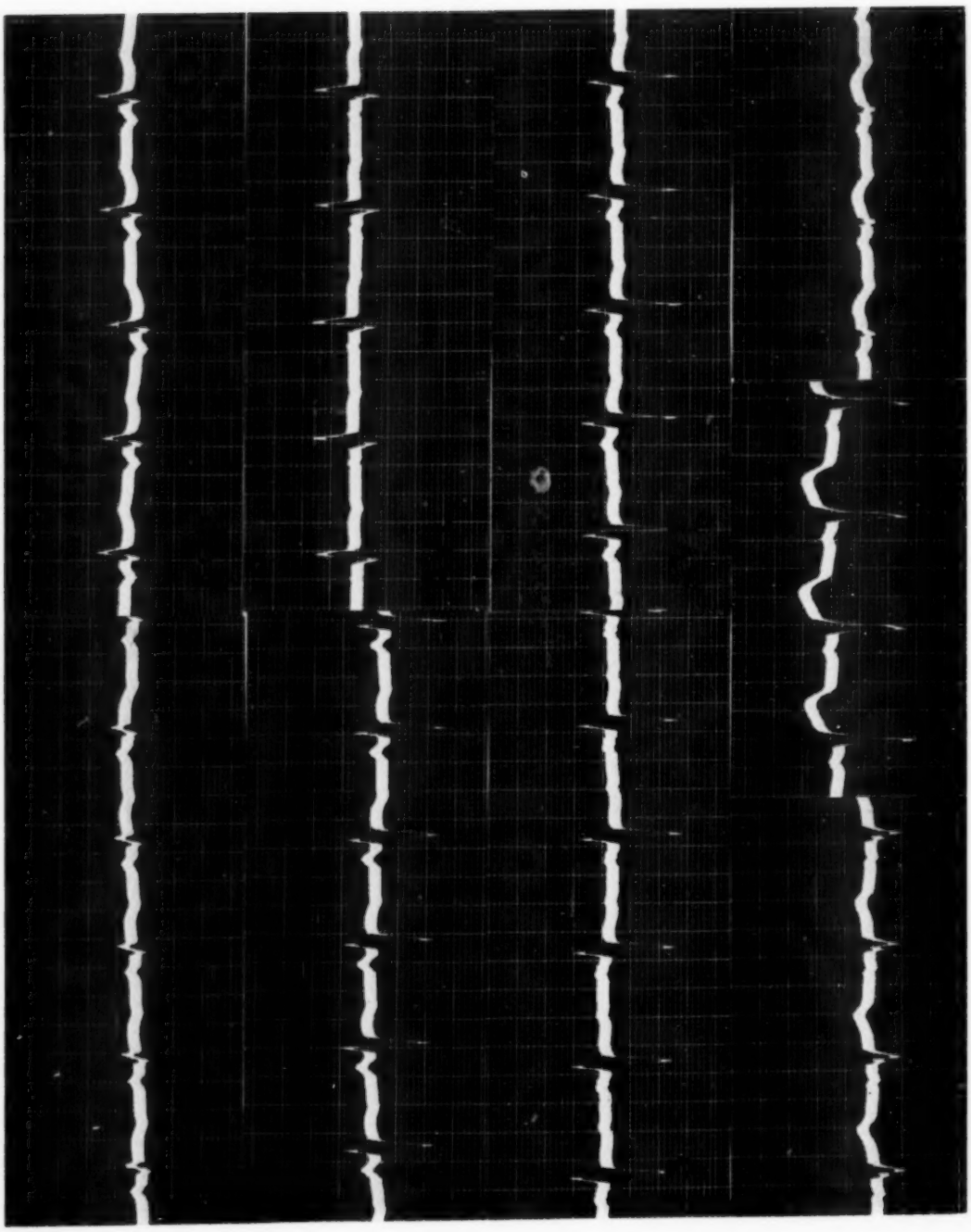

Fig. 3.—Electrocardiogram on J. B. H. twenty hours after administration of overdose of procaine amide. Note that P-R, QRS, and Q-T intervals have returned to original levels and T waves of Fig. 2 now resemble those of initial tracing.

The patient was given no treatment during this period but was observed very closely. The following day he was asymptomatic and remained so until discharged from the hospital (Dec. 3, 1952). He was seen in the cardiac clinic Jan. 6, 1953 and continues to convalesce satisfactorily.

SUMMARY

A case of myocardial infarction has been presented in which ten times the prescribed dose of procaine amide (5.0 Gm.) was inadvertently administered. Recovery was uneventful and toxic symptoms disappeared eight hours later. No treatment was administered.

Fig. 3.—Electrocardiogram on J. B. H. twenty hours after administration of overdose of procaine amide. Note that P-R, QRS, and Q-T intervals have returned to original levels and T waves of Fig. 2 now resemble those of initial tracing.

CHRONIC AURICULAR TACHYCARDIA WITH UNUSUAL FEATURES

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INSTANCES of chronic auricular tachycardia, lasting for years are relatively common in the literature,[1-4] but a rather unusual type of arrhythmia was reported by Fine and Miller[5] and Miller and Perelman,[6] with distinctive characteristics. In these cases of ectopic auricular tachycardia, of large chronicity, there was a variation of the pulse rate induced by changes of posture, eventual atrioventricular block, electrical alternation, and absence of effect with carotid compression.

The tachycardia lasted for years without hemodynamic or subjective symptoms, and was stopped only temporarily by quinidine. In 1947, Gendel[7] reported two more cases, quite similar, both in young individuals free from cardiac disease in which the prominent feature was the continuous succession of short runs of auricular tachycardia alternating with groups of two or three normal beats.

In 1948, we published a similar case[8] and as we have followed this patient since 1944 and have collected one more case, we present here the observations for both.

CASE REPORTS

Case 1.—AMR, a 19-year-old white man, came under observation in 1944 because in a physical examination an arrhythmia was found. His family stated that since childhood a pulse irregularity was often found, without any complaint from the patient who had a good capacity for sports.

Physical examination revealed an athletic, well-proportioned young man with no other abnormality than an irregular pulse. The blood pressure was 110/72 mm. Hg, the chest roentgenogram was normal, the Wassermann and Kahn tests were negative, and erythrocite sedimentation low.

Since this examination we have followed this patient with repeated physical observations and many electrocardiograms. These remained unchanged, except during and immediately after physical exercise, when the pulse became normal but the arrhythmia was resumed with rest. As is seen in Fig. 1, the disturbance consists of recurring short runs of tachycardia, alternating with two or three normal beats.

The ventricular complexes are identical and show a semivertical position and no abnormality in any lead. There are two types of auricular waves. The normal ones, P, are negative in V_R, and V_L, positive in V_F and diphasic in Lead V_1. The P-R interval is 0.16 second and has all the characteristics of sinus P waves.

The other auricular waves, P_1, are positive in Lead V_L and isoelectric in V_R and V_F. Furthermore, they are much more pronounced in left precordial leads. The P_1-R interval is invariably 0.24 second. These are ectopic auricular waves.

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A most interesting feature of this case is the cyclic variation of the tachycardia. It always begins with relatively low frequency, reaches a high rate, and slows down at the end of the run. The R-R interval is from 0.52 to 0.40 second.

With change in posture, the heart rate varies, being higher when standing with an R-R interval of 0.36 second.

In rare instances we have found atrioventricular block. Intolerance of digitalis made it impossible to study the action of this drug. Quinidine sulfate was ineffective. The normal rhythm is observed in this patient with physical effort.

Case 2.—AD, a 32-year-old white man, was admitted to the surgical ward of the Medical School Hospital, Lisbon, to be operated upon for peptic ulcer. During the postoperative period a pulse irregularity was noted and the patient sent to the Medical Service, for cardiologic study. This case is a duplicate of the first one.

Except for the peptic ulcer, he had been healthy always. However, he had noted for a long time pulse arrhythmia.

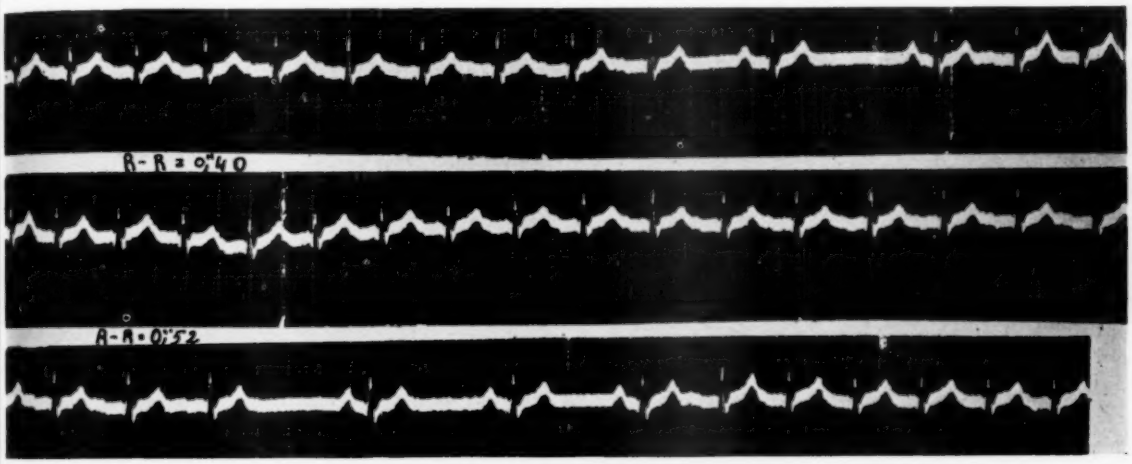

Fig. 1 (Case 1).—An uninterrupted record of Lead II, showing the beginning and the end of a tachycardial run. Note the different shape of P and P_1 and the variability of the R-R interval.

Physical examination failed to reveal any abnormality other than the arrhythmia. This disorder has, in the electrocardiograms, the same features referred to in Case 1. There are a succession of short runs of tachycardia and two sets of auricular waves. The P waves have normal characteristics and a P-R interval of 0.20 second. The P_1 waves are isoelectric in Leads V_R, V_L, and positive in V_F. The P_1-R interval is 0.28 second. Because of this length, the P_1 waves are seen frequently with the preceding T waves. The frequency of ectopic beats changes regularly in each run, beginning with R-R intervals of 0.64 second, speeding up to 0.43 second, then slowing at the end of the run. In some leads (V_1) slight electrical alternation is visible.

Digitalis reduces the frequency of these runs and provokes the appearance of atrioventricular block. Quinidine sulfate first changes the disturbance to a typical auricular bigeminism (Fig. 5) and later to a normal rhythm. With the stopping of the drug the chronic tachycardia reappears. The patient has been followed for twenty-six months, this disturbance being always present. However, he leads a normal life.

COMMENT

The common findings in the cases of Miller and Perelman, Gendel, and ourselves can be summarized as: (1) chronicity with absence of subjective symptoms and other evidence of cardiac disease; (2) variability with changes in the

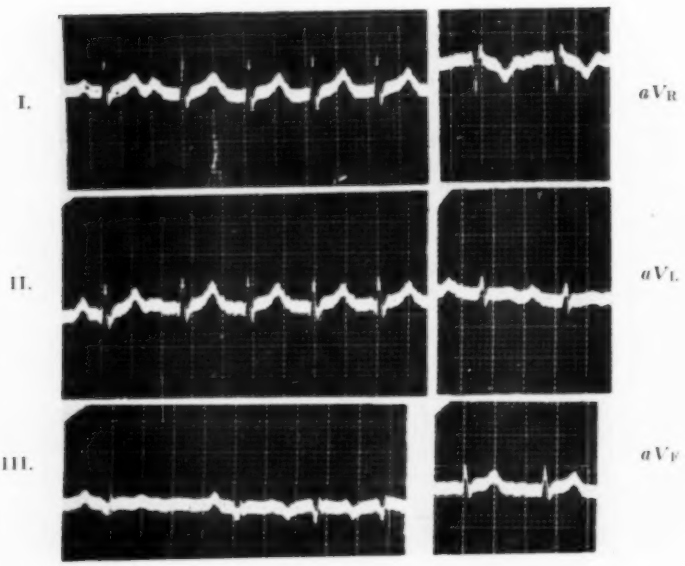

Fig. 2*A*.

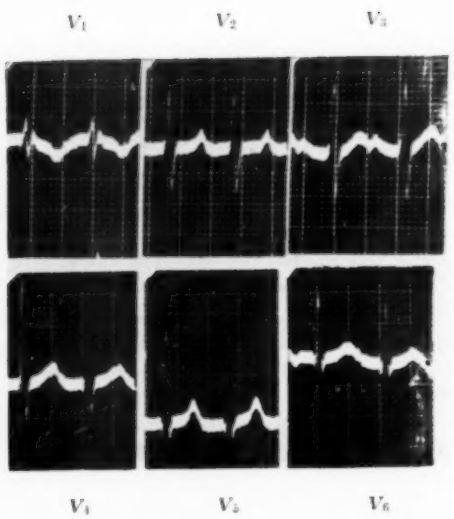

Fig. 2*B*.

Fig. 2 (Case 1).—*A*. and *B*. Standard and unipolar leads.

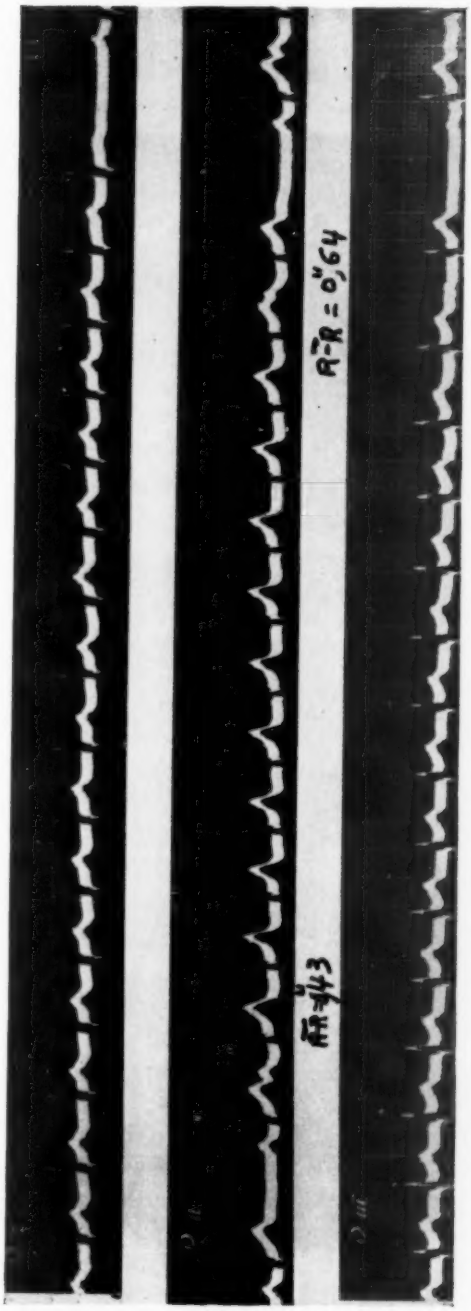

Fig. 3 (Case 2).—Standard leads. In Lead II, the beginning and the end of the tachycardial run are apparent. The variation of the rate is also marked, R-R distance changing from 0.43 to 0.64 second.

posture; (3) ectopic auricular origin; (4) no influence by carotid compression; and (5) frequent atrioventricular block.

In our patients, a curious finding, not so conspicuous in the others, is the cyclic variation in the rate of the tachycardia always regularly interrupted for some normal beats.

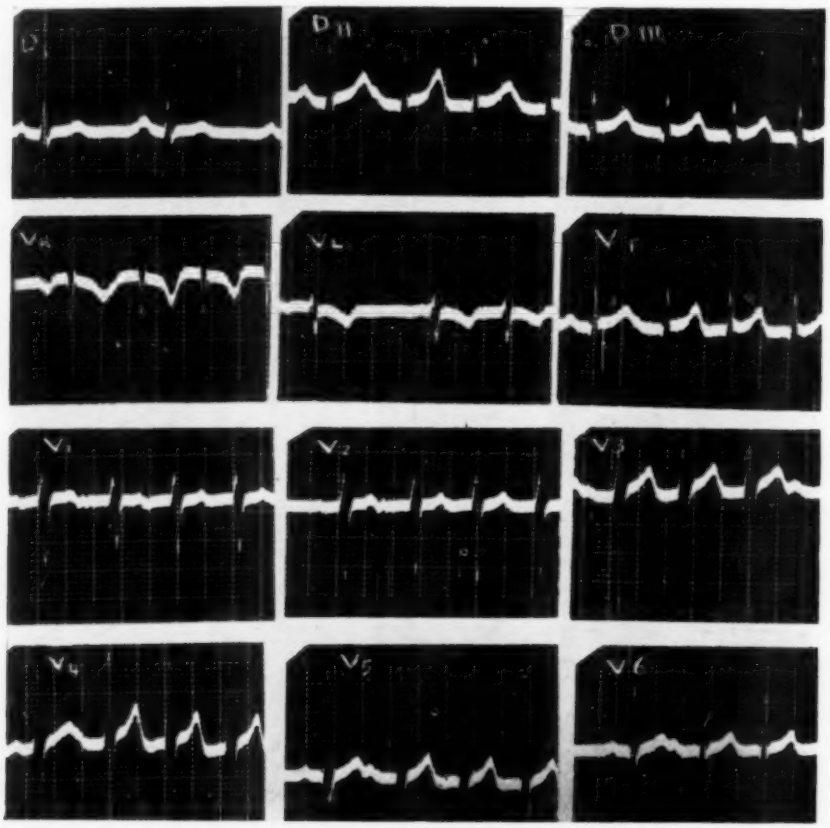

Fig. 4 (Case 2).—Standard and unipolar leads, showing the differences between P and P_1 and the P-R intervals.

We assume an ectopic origin, as did the preceding authors, on account of the anomalous shape of P_1 waves and the longer P_1-R intervals. This later feature, it was believed, would exclude a simple form of wandering pacemaker.

This P_1-R interval, longer than P-R, suggests also, in conjunction with the upright P_1 in V_F lead, an ectopic center located in the auricular appendix. In fact, Prinzmetal and associates[9] have recently given ample proof that extrasystoles originating in this zone of both right and left atria, have prolonged P_1-R intervals and positive P_1 waves in Leads II, III and V_F.

Prior to this work, Miller has expressed the opinion that this form of tachycardia cannot be explained by the circus movement hypothesis, in view of the long P_1-R intervals. Our second case would further indicate that this disturbance

is based upon a rapid succession of auricular extrasystoles, as we have been able to record instances of isolated premature beats.

However, we are unable to explain the cyclic variation of frequency and the postural changes present in our cases. These features, along with the chronicity without symptoms, justifies Miller's reasoning: "These two cases are so bizarre that doubt must arise as to whether they actually fall into the category of paroxysmal auricular tachycardia." In our first paper, we suggested the designation of "Miller's syndrome" for these rare cases which, we think, are somewhat different from the common auricular paroxysmal tachycardia.

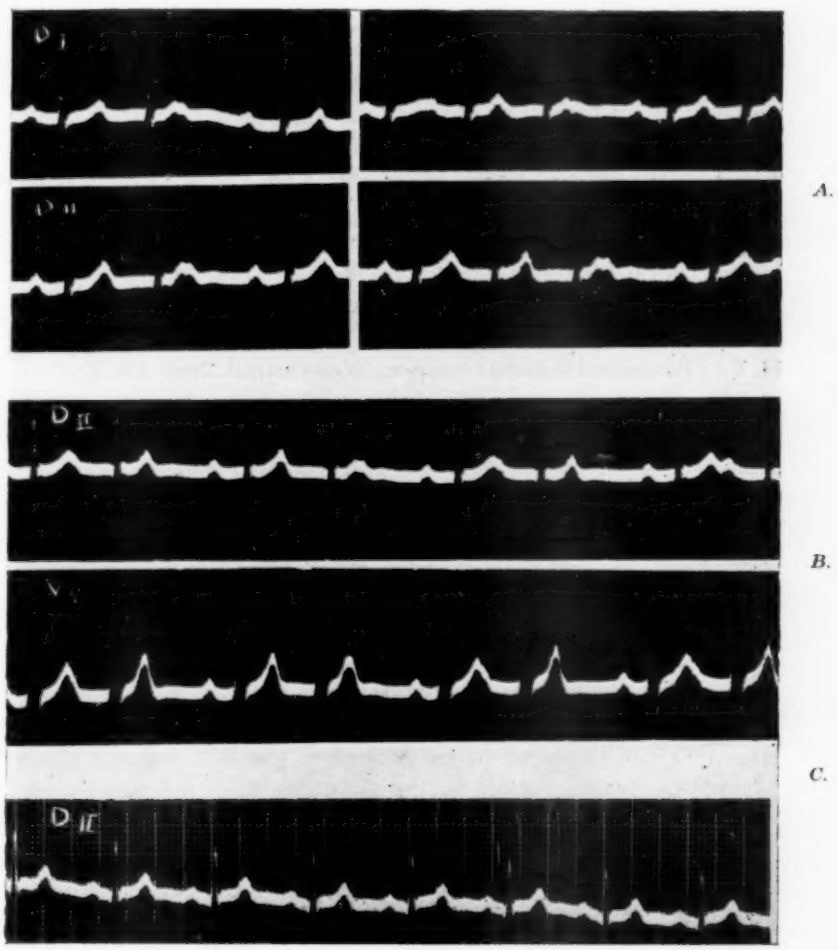

Fig. 5 (Case 2).—A. Atrioventricular block after administration of digitalis.

B. Auricular bigeminy after quinidine sulphate.

C. Normal rhythm after more prolonged action of quinidine.

SUMMARY

Two cases of chronic auricular tachycardia persistent over several years are presented. These cases have the following peculiarities: (1) a rhythm composed of short runs of ectopic auricular beats, alternating with two or three normal beats; (2) cyclic variability of the heart rate during these runs, always increasing first and then slowing in rate; (3) influence of body posture; (4) electrical alternation and atrioventricular block sometimes present.

There is discussed the analogy between these cases and those of Miller and Perelman and of Gendel. In view of their similarity, it is suggested that they belong in a special entity. A single ectopic focus, located in one of the auricular appendices, is suggested as the probable origin of the disturbance.

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THE DIAGNOSIS OF ORGANIC MITRAL STENOSIS IN THE PRESENCE OF SICKLE-CELL ANEMIA

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AS DEMONSTRATED by the patient described here, the differentiation of sickle-cell anemia from rheumatic heart disease with mitral stenosis may be impossible on clinical grounds alone. It has been demonstrated repeatedly that all the physical signs of mitral stenosis and regurgitation, including apical diastolic thrill, may be present on the basis of sickle-cell anemia alone. Repeatedly, suspicions of valvular heart disease have failed to be confirmed by post-mortem examination. The signs of mitral stenosis in sickle-cell anemia have been thought to be the result of left ventricular dilatation with relative mitral stenosis. Increased blood flow through the mitral orifice must exaggerate the relative mitral stenosis just as the torrential blood flow through the mitral orifice in cases of patent ductus arteriosus may produce a mitral diastolic murmur. Basilar diastolic murmurs in sickle-cell anemia may be due to pulmonic insufficiency from the pulmonary hypertension which frequently results from multiple pulmonary arteriolar thromboses. A true aortic diastolic murmur, if it really occurs on the basis of anemia alone, is difficult to explain. The differentiation of rheumatic heart disease from the heart of sickle-cell anemia is further confused by the difficulties of differentiating sickle-cell crisis from acute rheumatic fever and of differentiating the more low-grade manifestations of these two diseases.

The patient described below had severe sickle-cell anemia with classical physical signs of mitral stenosis. The case was reported by Klinefelter in 1942[1] as one of sickle-cell anemia simulating rheumatic heart disease. That the patient indeed had rheumatic heart disease with organic mitral stenosis in addition to sickle-cell anemia was strongly suggested before death by the demonstration of an elevated pulmonary capillary pressure. Autopsy confirmed the physiologic impression of organic mitral stenosis.

CASE REPORT

G.E. (J.H.H. 151230), a Negro woman, was born in 1920 and died in 1952. A brother died in sickle-cell crisis at the age of 31 with combined hepatic and renal failure. (The concentration of bilirubin in this patient's serum attained record-making levels for this hospital—125 mg. per 100 c.c.). Two brothers with the sickling trait and a sister without the sickling phenomenon are known to this hospital. In 1939 the patient was delivered of a boy who did not demonstrate sickling when studied in the first year of his life but has subsequently.

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In retrospect the patient's history appears to demonstrate an entanglement of rheumatic and sickle-cell manifestations which defy unraveling. Her eyes had been a yellowish-green hue as long as she could recall. At the age of three years she had the onset of frequent attacks of joint pains, fainting, and increase in the yellowness of the eyes. At nine years after a fainting spell at school she was told she had a bad heart. At thirteen years she had two ulcers on the right leg which healed slowly. At seventeen years she was demonstrated to be of low intelligence. At nineteen she was delivered of the child referred to above. Following delivery the patient developed a typical sickle-cell crisis with fever, leucocytosis, jaundice, and abdominal pain, and the diagnosis of sickle-cell anemia was made for the first time. Three months after delivery the patient returned to Gynecological Service for sterilization because of sickle-cell anemia and idiocy. After tubal ligation, what was interpreted as a mild crisis developed. She ran a low-grade fever which was believed to be caused by chronic tonsillitis (*beta* hemolytic streptococci were cultured from the throat), and tonsillectomy was performed two months after tubal ligation. During this period the patient demonstrated cardiac enlargement with a generalized systolic murmur, accentuated second pulmonic sound, and a prominent third heart sound but no definite diastolic murmurs.

The patient was then lost sight of until early in 1950, when she was thirty years old. During the interval she had had no severe crises. In February, 1950, she began to have frequent epistaxes. In March, 1950, she was admitted to the hospital in a sickle-cell crisis and severe congestive heart failure with a white blood cell count of 40,000 per $mm.^3$ The evidences of failure cleared in about two weeks but the liver, which had persistently enlarged to the level of the umbilicus, remained tender. Roentgenographic examination demonstrated numerous stones in the gall bladder, and the alkaline phosphatase was 20 Bodansky units per 100 c.c. Because of the suspicion that there might be an obstructive element in her jaundice, cholecystectomy was performed. The gall bladder contained about 50 multifaceted pigment stones. At no time following cholecystectomy did the alkaline phosphatase concentration of the serum fall below 20 Bodansky units per 100 c.c.

The patient was admitted next in August, 1950, in a sickle-cell crisis with pulmonary edema. At the time of this admission there were described for the first time (except for one occasion in April, 1950) the typical physical signs of mitral stenosis and regurgitation. A prominent diastolic rumble at the apex persisted when the hemoglobin was raised to 11.6 grams.

Thereafter, the patient continued to suffer from mild epistaxes and attacks of abdominal pain. The next admission was from December, 1950 to January, 1951, because of the development of severe cramping abdominal pain with some pain in the region of both knees. There was fairly marked icterus. The fundal vessels were very tortuous and redundant. The heart was enlarged to the anterior axillary line with a prominent apical impulse, and the pulmonic sounds were greatly accentuated. At the apex there was a rather high-pitched systolic murmur, and the second sound (there was no opening mitral snap) was followed by a low-pitched diastolic rumble which ended in a presystolic accentuation. This diastolic murmur was accompanied by a thrill. At times a soft protodiastolic decrescendo blow could be heard in the pulmonic area. The liver was two fingerbreadths below the right costal margin.

Hematologic findings revealed hemoglobin of 6.5 grams per cent and a white blood cell count of 17,000 with other findings typical of sickle-cell anemia: 2,000 nucleated red cells per cubic millimeter, sickle cells and target cells on smear, and 7.2 per cent reticulocytes. Serum bilirubin concentration was 7.2 mg. per cent, alkaline phosphatase 21.5 units. Prothrombin time was 50 per cent of normal. Maximum urine concentration attained on a Fishberg test was 1.016.

Phonocardiograms revealed a diastolic murmur (Fig. 1), but there was disagreement as to whether this had the configuration of that seen with organic mitral stricture. Electrocardiograms revealed right axis deviation. The progression of electrocardiographic changes over a period of thirteen years is shown in Fig. 2.

Roentgenograms of the chest (Fig. 3) revealed enlargement of the heart with a straight left heart border from a dilated pulmonary artery. No valvular calcification could be demonstrated. The findings were not considered entirely typical of mitral stenosis mainly because the left atrium seemed to be little, if any, enlarged. Review of the films indicates that the left atrium may have been larger than was appreciated. As seen in the illustration a faint second contour is visible just inside the right heart border. This probably represents a slightly enlarged left atrium. Roentgenkymograms with the esophagus filled with barium revealed no signs of systolic expansion waves of the type seen in mitral regurgitation.

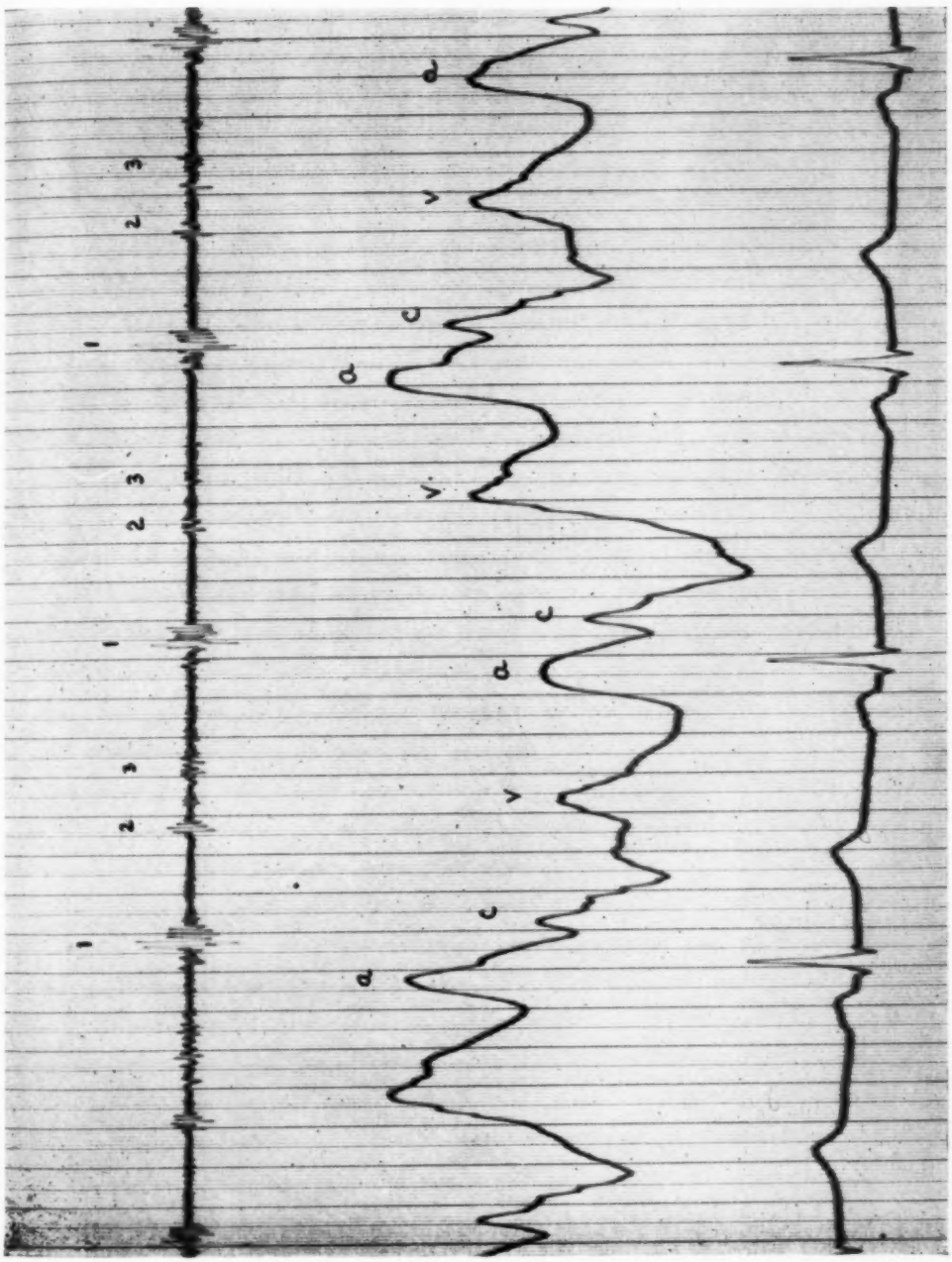

Fig. 1A.—Phonocardiograms, December, 1950. Recorded at apex from bell chest piece. Diastolic murmur between "3" and "1."

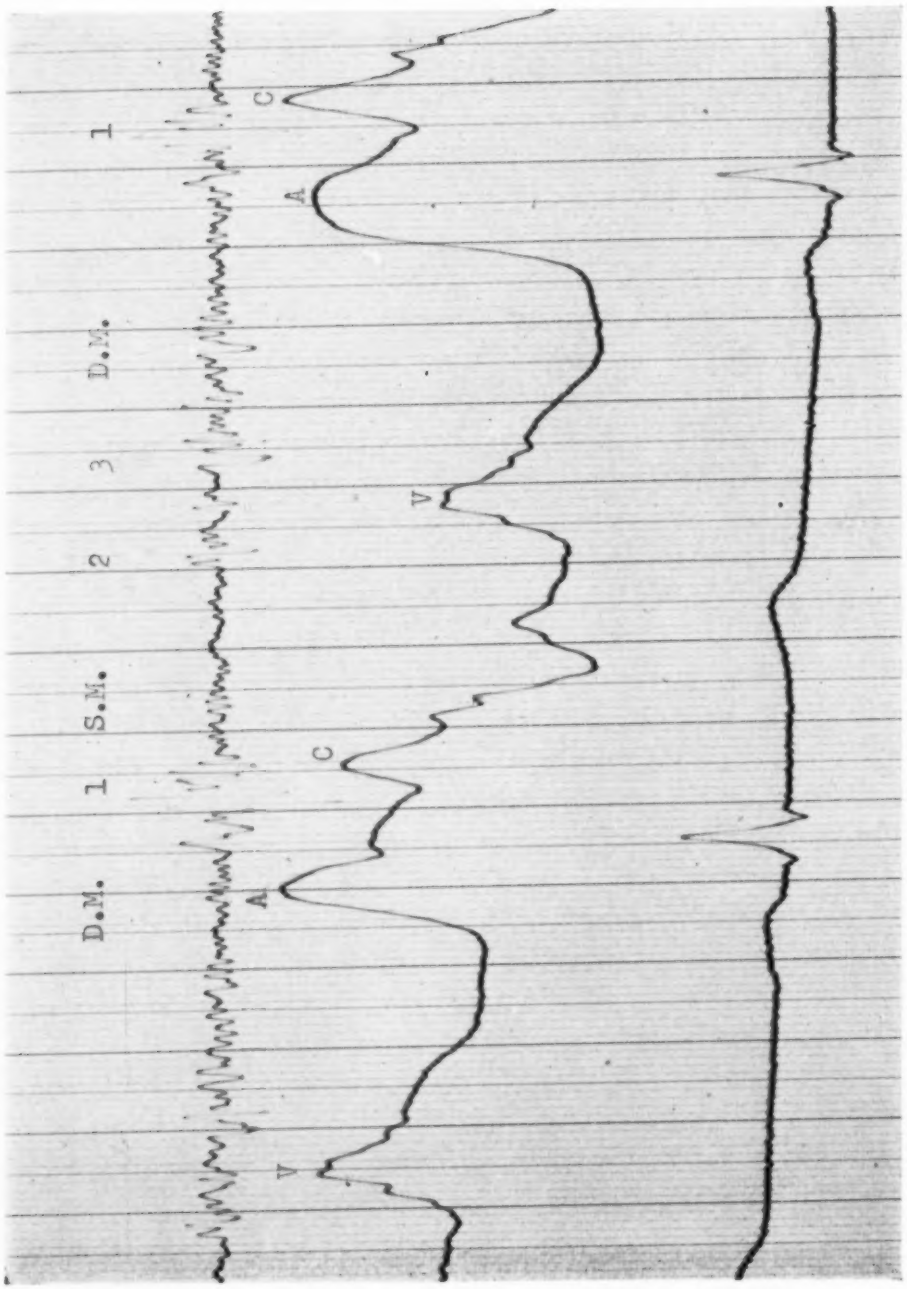

Fig. 1*B*.—Recorded at apex from diaphragm chest piece. *D.M.*=diastolic murmur. *S.M.*=systolic murmur. Jugular pulse in center in each case.

Many opinions were sought as to whether the patient had organic mitral stenosis. It was the opinion of most that although the physical signs were very suggestive—some questioned that they were entirely typical—of mitral stenosis, it was much more likely statistically that the signs were due to sickle-cell anemia alone.

On Dec. 28, 1950, cardiac catheterization was performed in the laboratory of Dr. Richard J. Bing in an attempt to answer the following questions:

(1) Is there evidence from the pulmonary capillary pressure determination to suggest that the patient does indeed have mitral stenosis?

(2) Is there in her failure an element of cor pulmonale of the type first demonstrated by Yater and Hansmann[2] in some of these cases?

(3) Is this "high output" failure, as is the rule when anemia plays a leading role?

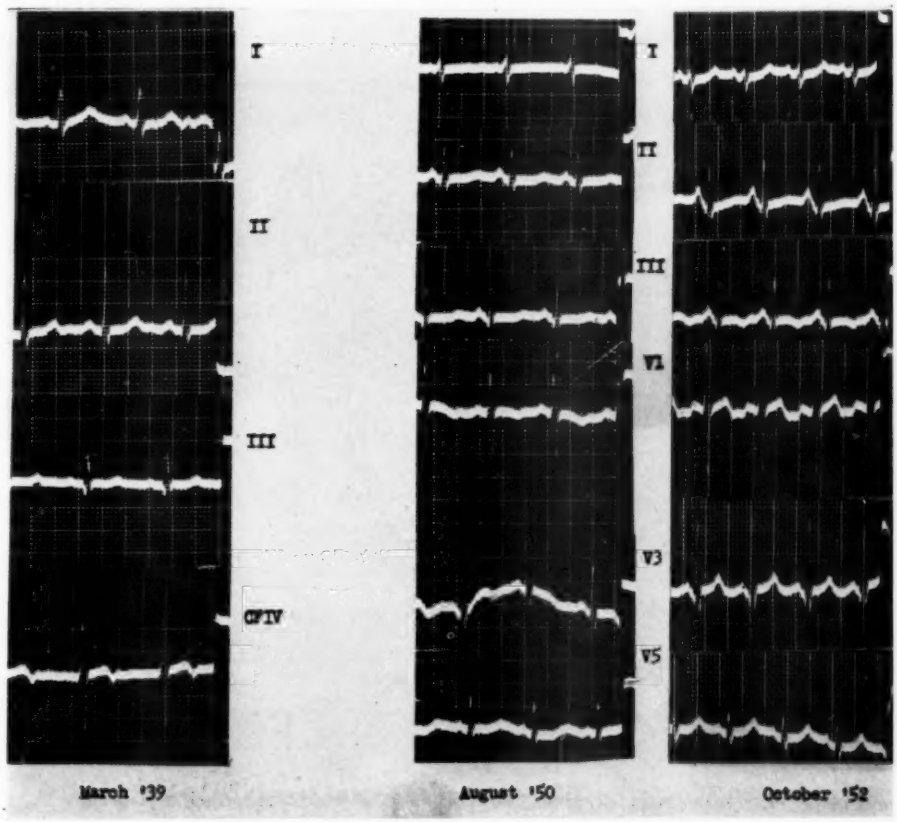

Fig. 2.—Electrocardiograms over 13 ½ years. The last tracing was taken three days before death. It is surprising that no more evidence of pericarditis is present.

At the time of catheterization blood oxygen capacity was about 60 per cent of normal. The pertinent results are as follows:

(1) The mean pulmonary capillary pressure was considerably elevated (23 mm. Hg).

(2) Pulmonary artery pressure was likewise elevated (60/24 mm. Hg) with further rise to 74/30 on mild exercise.

(3) Cardiac output was somewhat elevated (cardiac index = 3.9 L./min./m^2).

In April and in September, 1951, the patient had attacks of severe leg and abdominal pain requiring admission to the hospital. In November, 1951, and February, 1952, she was seen in the Out Patient Department in crises of moderate severity and given analgesics. She spent most of the last year of her life in bed because of persistent pains of at least mild intensity.

In September, 1952, the patient was again admitted for exacerbation of pain and for the last time in October, 1952. On this final occasion there was a reduplication of the second mitral sound with the second component presumed to represent an opening mitral snap. The other sounds and murmurs were as previously described and quite typical of mitral stenosis and regurgitation. There was a pronounced diastolic thrill at the apex. No pericardial friction rub was heard at any time. The manifestations appeared to be clearing at the usual rate when, one week after admission, the patient suddenly became dyspneic, went into shock, and died.

Autopsy (No. 23948) was performed by Dr. George McKinnon. The body weighed only 33 kilograms. All tissues were markedly icteric. The surface of the heart was covered by a thick shaggy layer of fibrinous exudate with some fibrous adhesions. The heart with its shaggy coat weighed 320 grams. The heart did not appear definitely enlarged except for some hypertrophy of the right ventricle. The main findings were in the left atrium and mitral valve. The endocardium of the left atrium was opaque. The mitral valve leaflets were thick, white, indurated, and fused producing narrowing of the mitral orifice, which was estimated to measure 0.5 cm. in

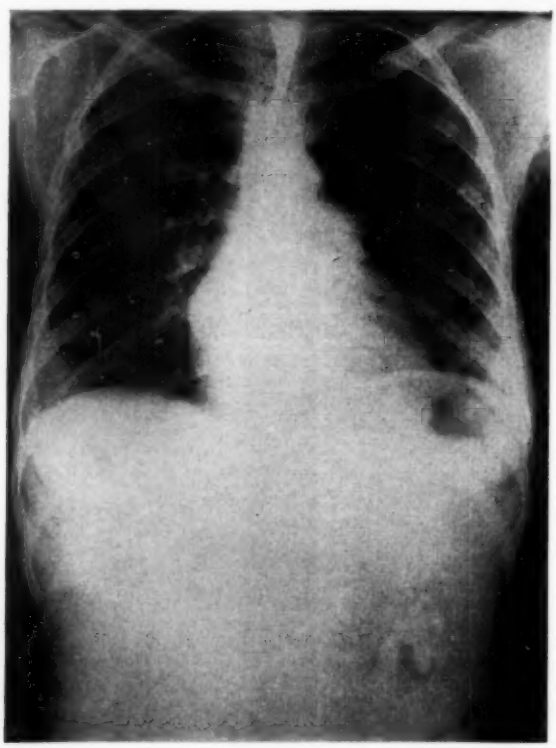

Fig. 3.—Posteroanterior radiograph of chest on January 4, 1951. On the right heart border a double contour is faintly visible, and the rest of the outline of the left atrium can be made out vaguely. This chamber appears large. The left heart border is straight.

diameter. The chordae were thickened and apparently shortened. The aortic valve seemed competent, but there was slight fusion of the left and posterior cusps with thickening of the margins. The myocardium was grossly normal in appearance. Hemolytic *Staphylococcus aureus* was cultured in large numbers from the blood of the heart. The liver showed a coarsely nodular cirrhosis. The spleen was tiny, weighing only 7 grams, and contained much golden brown pigment.

Histologically, the myocardium was found to show occasional perivascular scars but no fresh Aschoff bodies. The mitral cusps, their base, and the neighboring atrial endocardium were involved in a dense, nonspecific, hyaline scar. The pericarditis was clearly pyogenic with evidence

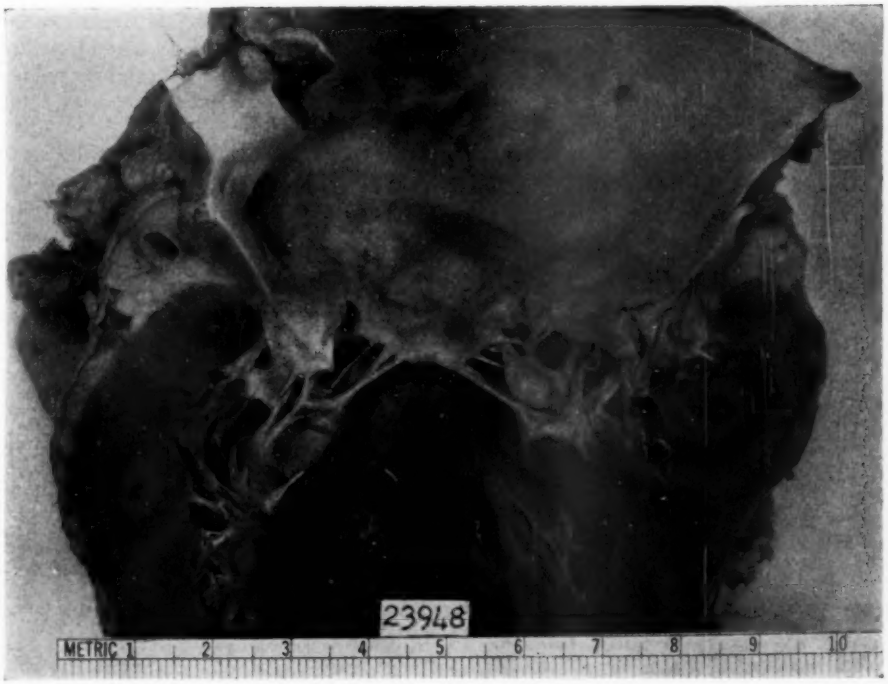

Fig. 4*A*. This and the next photograph provide documentation of the diseases associated in this patient. The thickening of the left atrial endocardium and of the mitral cusps and chordae is well demonstrated although the marked narrowing of the mitral orifice can be appreciated in part only.

Fig. 4*B*.—The small dimensions of the scarred, hemosiderotic spleen are demonstrated.

of subacute inflammation and numerous clumps of gram-positive cocci. The liver showed occasional tiny focal abscesses in which the same type of organism was stained. The lungs likewise showed occasional clumps of bacteria but no widespread infection. There was patchy pulmonary edema, large clumps of "heart failure cells" in some areas, and occasional pulmonary arterioles which revealed organizing thrombi.

The liver was extensively scarred with the main involvement being central. Bile casts were seen in many canaliculi, suggesting an element of obstruction consistent with the elevated alkaline phosphatase concentration of the serum. The spleen was scarred beyond histologic recognition with large deposits of hemosiderin. The kidneys showed extensive deposition of hemosiderin, atrophy of tubular epithelium, and areas of calcification.

The anatomical diagnoses were as follows: chronic rheumatic heart disease with mitral stenosis; sickle-cell anemia; subacute pericarditis due to hemolytic *Staphylococcus aureus*; focal abscesses in liver and lungs.

COMMENTS

Pulmonary capillary pressure is generally accepted[3] as a direct indicator of mean pressure in the pulmonary veins and left atrium although it is doubtful[8] that phasic changes of pressure in the left atrium are at all faithfully reflected. In view of the fact that the patient did not appear to be in heart failure at the time of cardiac catheterization (right atrial pressure was normal) left ventricular failure is unlikely as the cause of the elevation of pulmonary capillary pressure. Torrential blood flow through the mitral ring with relative mitral stenosis might conceivably result in some increase in pulmonary capillary pressure. In this patient, however, cardiac output was only slightly increased. For these reasons organic mitral stenosis seemed highly probable on the basis of the findings at catheterization.

The question is raised repeatedly as to whether disease of the pulmonary arterioles or capillaries can cause elevation of the "wedge" pressure (pulmonary capillary pressure). The writer knows of no evidence that such is the case with any regularity. In fact, the theory of the "wedge" pressure is now so well enforced by experimental evidence[3,8] that there is justification for questioning the result when elevated pulmonary capillary pressure is found in occasional cases of primary pulmonary vascular disease. The most common cause of artefactual elevation of pulmonary capillary pressure is probably the inadequate wedging of the catheter with incomplete occlusion of the pulmonary artery branch. Ankeney[8] has demonstrated that pulmonary capillary pressure recordings with significant phasic changes must be viewed with suspicion. The tracings of pulmonary capillary pressure in the patient described above revealed virtually no phasic changes. Of course, the pulmonary capillary pressure will not differentiate the site of obstruction beyond the pulmonary capillary, but there is no evidence for pulmonary venous disease in sickle-cell anemia in general or in this patient in particular.

Most cases of mitral stenosis show a low resting cardiac output.[4] That this patient demonstrated a cardiac output at least at the upper limit of normal is probably an expression of the combination of lesions—anemia and mitral stenosis. The right axis deviation and pulmonary hypertension might have been produced by the pulmonary vascular lesions of sickle-cell anemia. However, the elevated pulmonary capillary pressure could probably be explained only on the basis of organic mitral stenosis.

Only one other case of mitral stenosis and sickle-cell disease has come to our attention in this hospital. This patient died of influenza pneumonia at the age of 25 years. She had rheumatic mitral stenosis at post-mortem examination. The patient had a history of "thin blood" and of frequent attacks of vague abdominal and joint pains. The skull was high, the limbs long, and the fundal vessels very tortuous. Hemoglobin concentration was 10 grams per hundred cubic centimeters, and there was 20 per cent sickling in a sealed preparation after 8 hours. In spite of these findings it is likely that this was only sickle-cell trait and not sickle-cell anemia since clinically the serum bilirubin concentration was normal even in her terminal illness, and at autopsy the spleen did not reveal the characteristic changes,[6] and other lesions of the type seen in sickle-cell anemia were not discovered.

Many of the cases of long-standing sickle-cell anemia have minor thickening and excrescences of the valve cusps. This may be the result of the increased blood flow of chronic anemia and conceivably analogous to the valve lesions accompanying experimental arteriovenous fistulae.[5] There is no reason to believe that these minor alterations in the valves result in a significant functional abnormality.

Cases of cor pulmonale due to pulmonary arteriolar thrombosis in sickle-cell anemia have been seen in this hospital. Although none of these patients has been subjected to cardiac catheterization one would anticipate finding normal or reduced pulmonary capillary pressure values if determined at a time when the patient was not in left ventricular failure.

Recently Plachta and Speer[7] found in the literature four "acceptable instances" of the association of rheumatic heart disease and sickle-cell anemia and added a fifth of their own. The patient described here is a sixth case.

SUMMARY

A case of sickle-cell anemia is reported in which the presence of organic mitral stenosis (proved at necropsy) was strongly suspected clinically as a result of the finding of elevated pulmonary capillary pressure on cardiac catheterization.

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Book Reviews

LEHRBUCH DER KRANKHEITEN DES HERZENS UND DER BLUTSTROMBAHN. By Fritz Lange. Stuttgart, 1953, Ferdinand Enke, 631 pages with 192 figures.

The book is an attempt to bring E. von Romberg's *Lehrbuch der Herz-und Gefässkrankheiten* (1925) up to date. Of this goal, however, the author falls considerably short. Heart catheterization and heart surgery are mentioned in the preface among the new developments since the last edition of von Romberg's textbook. From this, one might expect some detailed information on these subjects, but the reader will find very little of it. The discussion of surgical treatment of heart and vascular diseases takes five pages and that of heart catheterization about two in a volume of over 600 pages. No details of technique, normal standards of right auricular, ventricular or pulmonary arterial pressure are given or their deviations in the various abnormal conditions. The average physician will probably get no more information about heart catheterization or heart surgery from the book than he knew before.

Other important new developments are not even mentioned, for instance, ballistocardiography or photokymography; and x-ray kymography is limited to about one page of text and one figure. Also ignored is the large material on the role of cholesterol and related substances in the development of arteriosclerotic heart disease.

The first part of the book is introductory, and the second is devoted to methods (about 100 pages), but their selection is somewhat arbitrary. For determination of the minute and stroke volume Brömser's method, based on measurement of arterial pulse curves, is discussed in greater detail than the gas analytic methods. Brömser's method, to the best knowledge of this reviewer, has hardly been used outside Germany and its validity is debated even there (though not in this book).

On the other hand, the detailed description of a new method "Combinotonograph" designed for blood pressure measurements takes more space than heart catheterization. No results of any kind obtained with this method are given. The best part of this section is electrocardiography which includes also a discussion of spatial vectors.

The third and largest section includes the diseases of the heart (pp. 106 to 362) except congenital heart disease which is treated separately in the fourth section. Vascular regulations and vascular diseases are discussed in the fifth and sixth sections (pp. 397 to 540), while the last section is devoted to correlations between cardiovascular disease and other disorders.

In the chapters on heart disease (sections III and IV), considerable space is devoted to electrocardiography, which has become in Germany as essential for clinical diagnosis as in this country. The condensed discussion of arrhythmias (pp. 246 to 275) is quite satisfactory as an introduction to a rather complex subject. A definite tendency to overinterpretation of some of the electrocardiograms is noticeable. For instance, the electrocardiograms in Figs. 84 and 85 are shown as illustration of early left ventricular hypertrophy in a case of arterial hypertension and a case of aortic stenosis, but these electrocardiograms are entirely within the normal limits. The interpretation of the electrocardiogram in Fig. 110 as due to subendocardial infarct is not convincing. It shows T inversion without QRS changes in the anterior precordial leads, but this can be observed also in coronary insufficiency or pericarditis. Important would be post-mortem data, but neither in this nor in the other cases of myocardial infarct presented as illustrations is given such autopsy material.

Some statements in the book are not critical or not sufficiently documented. The hypothesis that a spasm of the coronary arteries is the underlying cause of angina pectoris is presented as the accepted opinion (p. 226). Some supporting evidence but none of the objections to this hypothesis are given, and the reader does not get the impression that this hypothesis is still very controversial. On the same page the opinion is advanced that the radiation of angina pectoris pain into the left arm is propagated by the arteries. The small heart in pulmonary tuberculosis is explained

with the action of some toxins, and the only question not yet decided is which toxins are responsible (p. 437). This is, of course, pure speculation, but it is not presented as such, and in some instances it will be difficult for the reader who is not experienced in this field to differentiate between opinions and facts.

In spite of the serious defects of this book, some of the detail is of definite interest for the American reader. It affords a comparison between current American and German concepts of disease and methods of treatment. A few arbitrarily selected examples may suffice for illustration.

A statistical analysis of the incidence of endocarditis lenta in Germany from 1935 to 1949 is given, based on nearly 600 cases. There was an abrupt increase of the incidence as well as mortality beginning from 1944, reaching its peak in 1948 with thirteen times as many cases as in 1945 (Fig. 46). Since then, the incidence is slowly decreasing. It was greatest among German war prisoners, who comprise 35 per cent of all cases, far in excess of their number in the general population. This confirms German experience after the First World War. It is suggested that malnutrition and exposure are contributing factors for endocarditis lenta, but the long latent period is somewhat puzzling. Penicillin treatment reduced the mortality from 87 per cent to 65 per cent.

Diphtheritic heart disease is given a greater space than that in comparable American textbooks, because of the much greater incidence of diphtheria in Germany. The electrocardiogram was abnormal in 53 per cent of all patients, in 75 per cent of patients with medium grade of diphtheria, and in 90 per cent of the serious cases. The early electrocardiographic changes are auricular arrhythmias. It is of prognostic interest that the electrocardiographic changes associated with the following myocarditis (atrioventricular block, S-T and T-wave changes) usually precede the clinical manifestations by ten days. They also are persistent for several months or years after clinical recovery. Death is, as a rule, due to ventricular fibrillation.

Balneological treatment of cardiovascular disease has always found greater emphasis in Germany than in other countries, probably explained by the availability of a rather large number of resorts. It is consistent with this tradition that for the treatment of angina pectoris warm arm and hand baths with temperature gradually rising up to 41°C. or as high as the patient will tolerate are "warmly" recommended. The use of quinidine is much more conservative than it is generally in the United States, cardiac decompensation being considered as contraindication.

Wuhrmann's (*Schweiz. med. Wchnschr.* **80**: 715, 1950) differentiation between myocarditis and "myocardosis" is accepted, the latter representing degeneration of the myocardial fibers without cellular infiltrations, secondary to metabolic disorders or electrolyte imbalance (chronic diseases of liver and kidneys, coma diabeticum, hepaticum and apoplecticum, malnutrition, chronic intestinal diseases, infections, etc.). Myocardosis produces electrocardiographic changes in 96 per cent of the cases, but the changes are not specific.

The book is written mainly for the medical student and practitioner. Its merit is a very fluid and very readable presentation, at the expense of a more critical and scholarly treatment.

E.S.

CONGENITAL HEART DISEASE. By Henning Goetsche. Copenhagen, 1952, Henning Goetsche.

This work is a thesis based upon 201 consecutive cases of congenital heart disease admitted to the Medical Department "B," of the University Hospital, in Copenhagen, February, 1947, to July, 1949. The patients were primarily selected for examination regarding surgical treatment. They were thoroughly studied with contrast media and catheterization and the study is largely a statistical analysis of the data thus obtained. Among them were 13 cases of coarctation of the aorta, 14 of isolated stenosis of the pulmonic valve, 24 of patent ductus arteriosus, 17 of interventricular septal defect with arteriovenous shunt, 10 of interventricular septal defect with mixed shunt, and 61 cases of tetralogy of Fallot.

The compilation of details renders the book a valuable reference work for anyone working in the field. The material is from the leading cardiovascular clinic in Denmark.

Each group of malformations is considered separately, including a discussion of the pathologic physiology, based upon information obtained from the literature and from the author's experience. The observed data are then presented, condensed in tables whenever suitable. Each chapter closes with a general discussion of the condition.

The work presents no new or startling findings and confines itself to an analysis of data obtained by the now generally accepted methods of investigation. The translation into English is practically flawless.

J.J.

CLINICAL CARDIOLOGY, by Franklin C. Massey and 33 Collaborators, Baltimore, 1953, Williams & Wilkins Company, 1,100 pages.

Clinical Cardiology is written by a group of well-qualified cardiologists, several of whom are drawn from Hahnemann Medical College, Philadelphia. The result is a concise and well-arranged compilation of known facts about heart disease and related subjects. In appeal and scope the book takes a place somewhere between Paul White's *Heart Disease* and Friedberg's *Diseases of the Heart* on one side and Stroud's *Diagnosis and Treatment of Cardiovascular Disease* on the other.

The work is arranged along orthodox lines, considering first the normal anatomic and physiologic aspects of the heart, including means of diagnosis, such as roentgenology and electrocardiography. Then follows consideration of the various aspects of clinical heart disease, rather as separate entities than according to a definite integrated plan. The book presents, therefore, more a series of essays than a progressive story. However, in its essay form it covers the majority of cardiologic subjects to which most internists would wish to refer. This reviewer has not read the book in its entirety but has seen enough to form the opinion that this is an excellent work both for reading and reference.

J. J.

Announcements

THE LIFE INSURANCE MEDICAL RESEARCH FUND will receive applications for awards available July 1, 1954, as follows: (1) Postdoctoral research fellowships, until Oct. 31, 1953. Preference is given to those who wish to work on cardiovascular function and disease or related fundamental problems. Stipends vary from $3,300 to $4,500. (2) Grants to institutions in aid of research on cardiovascular problems, until Nov. 15, 1953. Support is available for physiologic, biochemical, and other basic work broadly related to cardiovascular problems as well as for clinical research in this field. Further information and application forms may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 345 East 46th Street, New York 17, N. Y.

THE ENDOCRINE SOCIETY AND THE UNIVERSITY OF MINNESOTA announce a Postgraduate Assembly in Endocrinology and Metabolism for Physicians, the Sixth Annual Assembly sponsored by The Endocrine Society, which will be presented on the University of Minnesota campus from Sept. 28 to Oct. 3, 1953. Lectures will be held in the Museum of Natural History Auditorium, while the facilities of the immediately adjacent Center for Continuation Study will be available for demonstrations and for the accommodation of registrants for the course.

All aspects of clinical endocrinology and metabolism will be taken up, and recent important advances in the field will be stressed. Informative demonstrations and illustrative clinical cases will be presented, and ten panel discussions will provide registrants with opportunities to bring up special problems and questions. Each registrant will receive a booklet containing abstracts of all lectures.

Faculty for the Assembly includes outstanding authorities in the field of endocrinology from various parts of the country as well as members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. The program will be presented under the direction of Dr. Edward C. Reifenstein, Jr., General Chairman for The Endocrine Society, and Dr. C. J. Watson, Professor and Head, Department of Medicine. Chairman of local arrangements on behalf of The Endocrine Society is Dr. Edmund B. Flink.